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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Cyclic Urea Derivatives, Pharmaceutical Compositions Comprising These Compounds and Processes for Their Preparation

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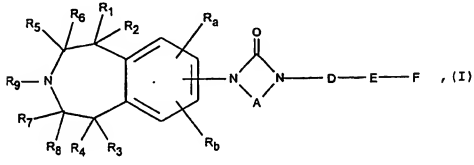
Abstract

The present invention relates to cyclic urea derivatives of general formula



wherein,

R_1 to R_9, R_a, R_b, A, D, E and F are as defined in claim 1, the tautomers thereof, the stereoisomers thereof, including the mixtures and salts thereof, particularly the physiologically acceptable salts with inorganic or organic acids or bases, which have, inter alia, valuable pharmacological properties, preferably aggregation-inhibiting effects, and to pharmaceutical compositions containing these compounds, the use thereof and processes for preparing them.

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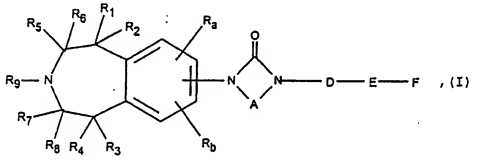
PCT-Text

Cyclic urea derivatives, pharmaceutical compositions comprising these compounds and processes for their preparation

The invention relates to cyclic urea derivatives of general formula



the tautomers, stereoisomers, including mixtures thereof, and the salts thereof, particularly their physiologically acceptable salts with inorganic or organic acids or bases, which have valuable pharmacological properties, preferably aggregation-inhibiting effects, pharmaceutical compositions comprising these compounds, their use and processes for their preparation.

In general formula I above, with the proviso that at least one of conditions (i) to (vi) below must be met

i) A denotes a mono- or di-alkyl substituted straight-chained C_{2-3}-alkylene group wherein a methylene group may be replaced by a carbonyl group, or denotes a -CH=N- group in which the hydrogen atom is replaced by an alkyl group,

ii) at least one of the groups R_1 to R_9 does not represent a hydrogen atom,

iii) R_9 denotes a cyclopropyl group, a C_{3-6}-alkenyl group substituted by an aryl group, or a C_{3-6}-alkynyl group optionally substituted by an aryl group, or a heteroarylalkyl group having 1 to 3 carbon atoms in the alkyl moiety, a 2,2,2-trifluoroethyl group, an alkyl group which is substituted by an alkoxy, cyano, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, amino, alkylamino, dialkylamino, alkylcarbonylamino, N-alkyl-alkylcarbonylamino, alkylsulphonylamino or N-alkyl-alkylsulphonylamino group, or R_9 denotes a C_{2-4}-alkyl group substituted by a carboxy or alkoxycarbonyl group, or R_9 denotes a C_{3-4}-alkyl group substituted by a hydroxy group,

iv) D denotes an optionally mono- or di-alkyl substituted C_{5-7}-cycloalkylene group, wherein a >CH- unit is replaced by a nitrogen atom and wherein additionally in the above-mentioned 5- to 7-membered rings a methylene group adjacent to a nitrogen atom may be replaced by a carbonyl group,

(v) E denotes a -CONH-alkylene, -CON(alkyl)-alkylene, -NHCO-alkylene or -N(alkyl)CO-alkylene group, wherein the alkylene moiety of the above-mentioned groups are optionally substituted by one or two alkyl groups or by an aryl or heteroaryl group, or E denotes an $-N(R_{14})$-alkylene group, wherein the alkylene moiety may additionally be substituted by one or two C_{1-6}-alkyl groups, by a C_{2-4}-alkenyl or C_{2-4}-alkynyl group, by a hydroxy, amino, aryl or heteroaryl group, by a C_{1-6}-alkoxy or C_{1-6}-alkylamino group, by a dialkylamino group having a total of 2 to 8 carbon atoms or by an HNR_{13} or N-alkyl-NR_{13} group,

vi) R_a does not denote a hydrogen atom,

then:

A denotes a straight-chained C_{2-3}-alkylene or C_{2-3}-alkenylene group which may be additionally substituted by one or two alkyl group or by a trifluoromethyl, aryl or arylalkyl group and wherein, additionally, a methylene group may be replaced by a carbonyl group,

a C_{5-7}-1,2-cycloalkylene or C_{5-7}-1,2-cycloalkenylene group which may be substituted by one or two alkyl groups,

a 1,2-arylene group,

a -CO-NH- or -NH-CO- group wherein the hydrogen in each case may be replaced by an alkyl, aryl or arylalkyl group, or a -CH=N- or -N=CH- group wherein the hydrogen atom in each case may be replaced by an alkyl, trifluoromethyl, aryl or arylalkyl group,

R_a and R_b, which may be identical or different, denote a hydrogen, fluorine, chlorine, brome or iodine atom, or an alkyl, trifluoromethyl, alkoxy or cyano group;

R_1 and R_3 independently of each other denote a hydrogen atom or an alkyl, aryl, hydroxy, alkoxy, cyano, carboxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl or dialkylaminocarbonyl group; and

R_2, R_4, R_6 and R_8 independently of one another each denote a hydrogen atom or an alkyl group, or

R_1 together with R_2 or R_3 together with R_4 denotes an oxygen atom;

R_5 and R_7 independently of each other denote a hydrogen atom or an alkyl, aryl, carboxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl or dialkylaminocarbonyl group;

R_9 denotes a hydrogen atom, a C_{1-8}-alkyl group, a

C_{3-7}-cycloalkyl group, a cycloalkylalkyl group having 3 to 7 carbon atoms in the cycloalkyl moiety and 1 to 3 carbon atoms in the alkyl moiety, an optionally aryl-substituted C_{3-6}-alkenyl group wherein the alkenyl group may not be connected to the nitrogen atom via the vinyl moiety, an optionally aryl-substituted C_{3-6}-alkynyl group in which the alkynyl group may not be connected to the nitrogen atom via the ethynyl moiety, an arylalkyl or heteroarylalkyl group each having 1 to 3 carbon atoms in the alkyl moiety, a hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkylcarbonylaminoalkyl, N-alkyl-alkylcarbonylaminoalkyl, alkylsulphonylaminoalkyl, N-alkyl-alkylsulphonylaminoalkyl, cyanoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, N-alkylaminocarbonylalkyl, N,N-dialkylaminocarbonylalkyl, alkoxycarbonyl, aryl-methyloxycarbonyl, formyl, acetyl, trifluoroacetyl, 2,2,2-trifluoroethyl, amidino or $R_{10}CO\text{-}O\text{-}(R_{11}CR_{12})\text{-}O\text{-}CO$- group, wherein

R_{10} denotes a C_{1-6}-alkyl group, a C_{5-7}-cycloalkyl group, an aryl or arylalkyl group having 1 to 3 carbon atoms in the alkyl moiety,

R_{11} denotes a hydrogen atom, an alkyl group, a C_{5-7}-cycloalkyl group or an aryl group, and

R_{12} denotes a hydrogen atom or an alkyl group;

D denotes an alkylene group,

an arylene group,

a C_{4-7}-cycloalkylene group optionally substituted by one or two alkyl groups,

an optionally mono- or di-alkyl substituted C_{5-7}-cycloalkylene group wherein a >CH- unit is replaced by a nitrogen atom, the

ring nitrogen atom being linked to a carbon atom of group E, and moreover in the above-mentioned 5- to 7-membered rings a methylene group adjacent to a nitrogen atom may be replaced by a carbonyl group;

E denotes a C_{1-6}-alkylene group which may be substituted by one or two C_{1-6}-alkyl groups, by a C_{2-4}-alkenyl or C_{2-4}-alkynyl group, by a hydroxy, amino, aryl or heteroaryl group, by a C_{1-6}-alkoxy or C_{1-6}-alkylamino group, by a dialkylamino group having a total of 2 to 8 carbon atoms, or by an HNR_{13}- or N-alkyl-NR_{13}- group, wherein

R_{13} denotes an alkylcarbonyl or alkylsulphonyl group each having 1 to 6 carbon atoms in the alkyl moiety, an alkyloxycarbonyl group having a total of 2 to 5 carbon atoms, a cycloalkylcarbonyl or cycloalkylsulphonyl group each having 5 to 7 carbon atoms in the cycloalkyl moiety, an arylalkylcarbonyl, arylalkylsulphonyl, arylalkoxycarbonyl, arylcarbonyl or arylsulphonyl group,

or E denotes an alkylene group linked to the group D via a group W, (wherein W denotes an oxygen or sulphur atom, or a sulphinyl, sulphonyl or -NR_{14}- group, wherein

R_{14} denotes a hydrogen atom, an alkyl group, a cycloalkyl, cycloalkylalkyl, cycloalkylcarbonyl or cycloalkylsulphonyl group each having 3 to 7 carbon atoms in the cycloalkyl moiety, or an aryl, heteroaryl, arylalkyl, heteroaryl-alkyl, alkylcarbonyl, alkylsulphonyl, arylcarbonyl, heteroarylcarbonyl, arylsulphonyl, or heteroarylsulphonyl group),

and the alkylene group may additionally be substituted by one or two C_{1-6}-alkyl groups, by an alkenyl or alkynyl group each having 2 to 4 carbon atoms, by a hydroxy, amino, aryl or heteroaryl group, by an alkoxy or alkylamino group each having

1 to 6 carbon atoms, by a dialkylamino group having a total of 2 to 8 carbon atoms, or by an HNR_{13}- or N-alkyl-NR_{13}- group, wherein the heteroatom of the additional substituent is separated from a heteroatom of the group W by at least 2 carbon atoms and R_{13} is as hereinbefore defined,

or E denotes a -CONH-alkylene, -CON(alkyl)-alkylene, -NHCO-alkylene or -N(alkyl)CO-alkylene group, wherein the alkylene moiety of the above-mentioned groups may be substituted in each case by one or two alkyl groups or by an aryl or heteroaryl group, and

F denotes a carbonyl group substituted by a hydroxy group, by a C_{1-8}-alkoxy group, by an arylalkoxy group or by an $R_{15}O$-group, wherein

R_{15} denotes a C_{4-7}-cycloalkyl group or a cycloalkylalkyl group having 3 to 7 carbon atoms in the cycloalkyl moiety, a C_{9-12}-benzocycloalkyl group or an aryl group,

or F denotes an $R_{16}CO\text{-}O\text{-}CHR_{17}\text{-}O\text{-}CO$ group, wherein

R_{16} denotes a C_{1-6}-alkyl or C_{1-6}-alkoxy group, a cycloalkyl or cycloalkyloxy group each having 5 to 7 carbon atoms in the cycloalkyl moiety, an aryl, aryloxy, arylalkyl or arylalkoxy group, and

R_{17} denotes a hydrogen atom or an alkyl group,

and the shortest distance between the group F and the nitrogen atom substituted by R_9 is at least 11 bonds;

whilst, unless otherwise specified,

any aryl moiety mentioned in the definition of the above-mentioned groups may be a phenyl group which may be monosubstituted by R_{18}, mono-, di- or trisubstituted by R_{19} or

monosubstituted by R_{18} and additionally mono- or disubstituted by R_{19}, wherein the substituents may be identical or different and

R_{18} denotes a cyano, carboxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonyl, alkylcarbonyl, alkylsulphenyl, alkylsulphinyl, alkylsulphonyl, alkylsulphonyloxy, perfluoroalkyl, perfluoroalkoxy, nitro, amino, alkylamino, dialkylamino, alkylcarbonylamino, phenylalkylcarbonylamino, phenylcarbonylamino, alkylsulphonylamino, phenylalkylsulphonylamino, phenylsulphonylamino, N-alkyl-alkylcarbonylamino, N-alkyl-phenylalkylcarbonyl-amino, N-alkyl-phenylcarbonylamino, N-alkyl-alkyl-sulphonylamino, N-alkyl-phenylalkylsulphonylamino, N-alkyl-phenylsulphonylamino, aminosulphonyl, alkylaminosulphonyl or dialkylaminosulphonyl group and

R_{19} denotes an alkyl, hydroxy or alkoxy group, or a fluorine, chlorine, bromine or iodine atom, whilst two groups R_{19}, provided that they are bound to adjacent carbon atoms, may also represent a C_{3-5}-alkylene group, a 1,3-butadiene-1,4-diylene group or a methylenedioxy group,

any arylene moiety mentioned in the definition of the above groups may be a phenylene group which may be monosubstituted by R_{18}, mono- or disubstituted by R_{19}, or monosubstituted by R_{18} and additionally monosubstituted by R_{19}, wherein the substituents may be identical or different and are defined as hereinbefore,

any heteroaryl moiety mentioned in the definition of the above groups may be a 5-membered heteroaromatic ring which contains an oxygen, sulphur or nitrogen atom, a nitrogen and an oxygen, sulphur or nitrogen atom, or two nitrogen atoms and an oxygen, sulphur or nitrogen atom, or a 6-membered heteroaromatic ring which contains 1, 2 or 3 nitrogen atoms and wherein

additionally one or two -CH=N- groups may each be replaced by a -CO-NH- group, wherein

the above-mentioned heteroaromatic rings may be substituted by one or two alkyl groups or, on the carbon skeleton, by a fluorine, chlorine, bromine or iodine atom, or by a hydroxy or alkoxy group,

and unless otherwise specified the above-mentioned alkyl, alkylene or alkoxy moieties may each contain 1 to 4 carbon atoms, and each carbon atom in the above-mentioned alkylene and cycloalkylene moieties is linked to at most one heteroatom,

and the tautomers, stereoisomers and salts thereof.

Preferred compounds of the above general formula I are (with the exception of

2-[trans-4-(2-carboxyethyl)cyclohexyl]-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-4H-1,2,4-triazol-3-one,

2-[trans-4-(2-carboxyethyl)cyclohexyl]-4-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-4H-1,2,4-triazol-3-one,

1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(3-cyclopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

1-[1-(2-carboxyethyl)-4-piperidinyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

1-[1-(2-carboxyethyl)-4-piperidinyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one and

1-[2-[(2-carboxyethyl)aminocarbonyl]ethyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

and with the proviso that at least one of the following conditions (i) to (vi) is satisfied

i) A denotes a mono- or di-alkyl substituted straight-chained C_{2-3}-alkylene group in which a methylene group may be replaced by a carbonyl group, or denotes a -CH=N- group in which the hydrogen atom is replaced by an alkyl group,

ii) at least one of the groups R_1 to R_8 does not represent a hydrogen atom,

iii) R_9 denotes a cyclopropyl group, a C_{3-6}-alkenyl group substituted by an aryl group, or a C_{3-6}-alkynyl group optionally substituted by an aryl group, or a heteroarylalkyl group having 1 to 3 carbon atoms in the alkyl moiety, a 2,2,2-trifluoroethyl group, an alkyl group which is substituted by an alkoxy, cyano, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, amino, alkylamino, dialkylamino, alkylcarbonylamino, N-alkyl-alkylcarbonylamino, alkylsulphonylamino or N-alkyl-alkylsulphonylamino group, or R_9 denotes a C_{2-4}-alkyl group substituted by a carboxy or alkoxycarbonyl group, or R_9 denotes a C_{3-4}-alkyl group substituted by a hydroxy group,

iv) D denotes an optionally mono- or di-alkyl substituted C_{5-7}-cycloalkylene group wherein a >CH- unit is replaced by a nitrogen atom and wherein additionally in the above-mentioned 5- to 7-membered rings a methylene group adjacent to a nitrogen atom may be replaced by a carbonyl group,

v) E denotes a -CONH-alkylene, -CON(alkyl)-alkylene, -NHCO-alkylene or -N(alkyl)CO-alkylene group the alkylene moiety of the above-mentioned groups optionally being substituted by one or two alkyl groups or by an aryl or heteroaryl group, or E denotes an -N(R_{14})-alkylene group wherein the alkylene moiety may additionally be substituted by one or two C_{1-6}-alkyl groups, by a C_{2-4}-alkenyl or C_{2-4}-alkynyl

group, by a hydroxy, amino, aryl or heteroaryl group, by a C_{1-6}-alkoxy or C_{1-6}-alkylamino group, by a dialkylamino group having a total of 2 to 8 carbon atoms, or by an HNR_{13} or N-alkyl-NR_{13} group,

vi) R_a does not denote a hydrogen atom),

those wherein:

A denotes a straight-chained C_{2-3}-alkylene or C_{2-3}-alkenylene group which may additionally be substituted by one or two alkyl groups or by a trifluoromethyl, aryl or arylalkyl group and wherein, additionally, a methylene group may be replaced by a carbonyl group,

a C_{5-7}-1,2-cycloalkylene or C_{5-7}-1,2-cycloalkenylene group which may be substituted by one or two alkyl groups,

a 1,2-arylene group,

a -CO-NH- or -NH-CO- group wherein the hydrogen in each case may be replaced by an alkyl, aryl or arylalkyl group, or a -CH=N- or -N=CH- group wherein the hydrogen atom in each case may be replaced by an alkyl, trifluoromethyl, aryl or arylalkyl group;

R_a and R_b, which may be identical or different, denote a hydrogen, fluorine, chlorine, brome or iodine atom, or an alkyl, trifluoromethyl, alkoxy or cyano group,

R_1 and R_3 independently of each other denote a hydrogen atom or an alkyl, aryl, hydroxy, alkoxy, cyano, carboxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl or dialkylaminocarbonyl group, and

R_2, R_4, R_6 and R_8 independently of one another each denote a hydrogen atom or an alkyl group, or

R_1 together with R_2 or R_3 together with R_4 denotes an oxygen atom,

R_5 and R_7 independently of each other denote a hydrogen atom or an alkyl, aryl, carboxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl or dialkylaminocarbonyl group,

R_9 denotes a hydrogen atom, a C_{1-8}-alkyl group, a C_{3-7}-cycloalkyl group, a cycloalkylalkyl group having 3 to 7 carbon atoms in the cycloalkyl moiety and 1 to 3 carbon atoms in the alkyl moiety, an optionally aryl-substituted C_{3-6}-alkenyl group wherein the alkenyl group may not be connected to the nitrogen atom via the vinyl moiety, an optionally aryl-substituted C_{3-6}-alkynyl group in which the alkynyl group may not be connected to the nitrogen atom via the ethynyl moiety, an arylalkyl or heteroarylalkyl group each having 1 to 3 carbon atoms in the alkyl moiety, a hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkylcarbonylaminoalkyl, N-alkyl-alkylcarbonylaminoalkyl, alkylsulphonylaminoalkyl, N-alkyl-alkylsulphonylaminoalkyl, cyanoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, N-alkyl-aminocarbonylalkyl, N,N-dialkyl-aminocarbonylalkyl, alkoxycarbonyl, arylmethyloxycarbonyl, formyl, acetyl, trifluoroacetyl, 2,2,2-trifluoroethyl, or amidino group, or a $R_{10}CO\text{-}O\text{-}(R_{11}CR_{12})\text{-}O\text{-}CO$- group, wherein

R_{10} denotes a C_{1-8}-alkyl group, a C_{5-7}-cycloalkyl group, or an aryl or arylalkyl group having 1 to 3 carbon atoms in the alkyl moiety,

R_{11} denotes a hydrogen atom, an alkyl group, a C_{5-7}-cycloalkyl group or an aryl group, and

R_{12} denotes a hydrogen atom or an alkyl group;

D denotes an alkylene group,

an arylene group,

a C_{4-7}-cycloalkylene group optionally substituted by one or two alkyl groups,

an optionally mono- or di-alkyl substituted C_{5-7}-cycloalkylene group wherein a >CH- unit is replaced by a nitrogen atom, the ring nitrogen atom being linked to a carbon atom of group E, and moreover in the above-mentioned 5- to 7-membered rings a methylene group adjacent to a nitrogen atom may be replaced by a carbonyl group;

E denotes a C_{1-6}-alkylene group which may be substituted by one or two C_{1-6}-alkyl groups, by a C_{2-4}-alkenyl or C_{2-4}-alkynyl group, by a hydroxy, amino, aryl or heteroaryl group, by a C_{1-6}-alkoxy or C_{1-6}-alkylamino group, by a dialkylamino group having a total of 2 to 8 carbon atoms, or by an HNR_{13}- or N-alkyl-NR_{13}- group, wherein

> R_{13} denotes an alkylcarbonyl or alkylsulphonyl group each having 1 to 6 carbon atoms in the alkyl moiety, an alkyloxycarbonyl group having a total of 2 to 5 carbon atoms, a cycloalkylcarbonyl or cycloalkylsulphonyl group each having 5 to 7 carbon atoms in the cycloalkyl moiety, an arylalkylcarbonyl, arylalkylsulphonyl, arylalkoxycarbonyl, arylcarbonyl or arylsulphonyl group,

or E denotes an alkylene group linked to the group D via a group W (wherein W denotes an oxygen or sulphur atom, or a sulphynyl, sulphonyl or -NR_{14}- group, wherein

> R_{14} denotes a hydrogen atom, an alkyl group, a cycloalkyl, cycloalkylalkyl, cycloalkylcarbonyl or cycloalkylsulphonyl group each having 3 to 7 carbon atoms in the cycloalkyl moiety, or an aryl, heteroaryl, arylalkyl, heteroaryl-alkyl, alkylcarbonyl, alkylsulphonyl, arylcarbonyl, heteroarylcarbonyl, arylsulphonyl, or heteroarylsulphonyl

group),

and the alkylene group may additionally be substituted by one or two C_{1-6}-alkyl groups, by an alkenyl or alkynyl group each having 2 to 4 carbon atoms, by a hydroxy, amino, aryl or heteroaryl group, by an alkoxy or alkylamino group each having 1 to 6 carbon atoms, by a dialkylamino group having a total of 2 to 8 carbon atoms, or by an HNR_{13}- or N-alkyl-NR_{13}- group, wherein the heteroatom of the additional substituent is separated from a heteroatom of the group W by at least 2 carbon atoms and R_{13} is as hereinbefore defined,

or E denotes a -CONH-alkylene, -CON(alkyl)-alkylene, -NHCO-alkylene or -N(alkyl)CO-alkylene group, wherein the alkylene moiety of the above-mentioned groups may be substituted in each case by one or two alkyl groups or by an aryl or heteroaryl group; and

F denotes a carbonyl group substituted by a hydroxy group, by a C_{1-8}-alkoxy group, by an arylalkoxy group or by an $R_{15}O$-group, wherein

R_{15} denotes a C_{4-7}-cycloalkyl group or a cycloalkylalkyl group having 3 to 7 carbon atoms in the cycloalkyl moiety, a C_{9-12}-benzocycloalkyl group or an aryl group,

or F denotes an $R_{16}CO\text{-}O\text{-}CHR_{17}\text{-}O\text{-}CO$ group, wherein

R_{16} denotes a C_{1-6}-alkyl or C_{1-6}-alkoxy group, a cycloalkyl or cycloalkyloxy group each having 5 to 7 carbon atoms in the cycloalkyl moiety, an aryl, aryloxy, arylalkyl or arylalkoxy group, and

R_{17} denotes a hydrogen atom or an alkyl group,

and the shortest distance between the group F and the nitrogen atom substituted by R_9 is at least 11 bonds,

whilst, unless otherwise specified,

any aryl moiety mentioned in the definition of the above-mentioned groups may be a phenyl group which may be monosubstituted by R_{18}, mono-, di- or trisubstituted by R_{19}, or monosubstituted by R_{18} and additionally mono- or disubstituted by R_{19}, wherein the substituents may be identical or different and

R_{18} denotes a cyano, carboxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonyl, alkylcarbonyl, alkylsulphenyl, alkylsulphinyl, alkylsulphonyl, alkylsulphonyloxy, perfluoroalkyl, perfluoroalkoxy, nitro, amino, alkylamino, dialkylamino, alkylcarbonylamino, phenylalkylcarbonylamino, phenylcarbonylamino, alkylsulphonylamino, phenylalkylsulphonylamino, phenylsulphonylamino, N-alkyl-alkylcarbonylamino, N-alkyl-phenylalkylcarbonyl-amino, N-alkyl-phenylcarbonylamino, N-alkyl-alkyl-sulphonylamino, N-alkyl-phenylalkylsulphonylamino, N-alkyl-phenylsulphonylamino, aminosulphonyl, alkylaminosulphonyl or dialkylaminosulphonyl group, and

R_{19} denotes an alkyl, hydroxy or alkoxy group, or a fluorine, chlorine, bromine or iodine atom, whilst two groups R_{19}, provided that they are bound to adjacent carbon atoms, may also represent a C_{3-5}-alkylene group, a 1,3-butadien-1,4-diylene group or a methylenedioxy group,

any arylene moiety mentioned in the definition of the above groups may be a phenylene group which may be monosubstituted by R_{18}, mono- or disubstituted by R_{19}, or monosubstituted by R_{18} and additionally monosubstituted by R_{19}, wherein the substituents may be identical or different and are defined as hereinbefore,

any heteroaryl moiety mentioned in the definition of the above groups may be a 5-membered heteroaromatic ring which contains an oxygen, sulphur or nitrogen atom, a nitrogen and an oxygen, sulphur or nitrogen atom, or two nitrogen atoms and an oxygen, sulphur or nitrogen atom, or a 6-membered heteroaromatic ring which contains 1, 2 or 3 nitrogen atoms and wherein additionally one or two -CH=N- groups may each be replaced by a -CO-NH- group, wherein

the above-mentioned heteroaromatic rings may be substituted by one or two alkyl groups or, on the carbon skeleton, by a fluorine, chlorine, bromine or iodine atom, or by a hydroxy or alkoxy group,

and unless otherwise specified the above-mentioned alkyl, alkylene or alkoxy moieties may each contain 1 to 4 carbon atoms, and each carbon atom in the above-mentioned alkylene and cycloalkylene moieties is linked to at most one heteroatom,

and the tautomers, stereoisomers and salts thereof.

Particulary preferred compounds of the above general formula I are (with the exception of

2-[trans-4-(2-carboxyethyl)cyclohexyl]-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-4H-1,2,4-triazol-3-one,

2-[trans-4-(2-carboxyethyl)cyclohexyl]-4-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-4H-1,2,4-triazol-3-one,

1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(3-cyclopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

1-[1-(2-carboxyethyl)-4-piperidinyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

1-[1-(2-carboxyethyl)-4-piperidinyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one and

1-[2-[(2-carboxyethyl)aminocarbonyl]ethyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

and with the proviso that at least one of the following conditions (i) to (vi) is satisfied

(i) A denotes a $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CO-$ or $-COCH_2-$ group substituted by one or two methyl groups, or a $-C(CH_3)=N$ group,

(ii) at least one of the groups R_1 to R_8 does not denote a hydrogen atom,

(iii) R_9 denotes a cyclopropyl, cinnamyl or 2,2,2-trifluoroethyl group, a C_{3-4}-alkynyl group, a pyridylalkyl group having 1 to 3 carbon atoms in the alkyl moiety, or an alkyl group substituted by an alkoxy, cyano, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, amino, alkylamino, dialkylamino, alkylcarbonylamino, N-alkyl-alkylcarbonylamino, alkylsulphonylamino or N-alkyl-alkylsulphonylamino group, or R_9 denotes a C_{2-4}-alkyl group substituted by a carboxy or alkoxycarbonyl group, or a C_{3-4}-alkyl group substituted by a hydroxy group,

(iv) D denotes a 1,4-piperidinylene group optionally substituted by one or two methyl groups,

(v) E denotes an $-N(R_{14})$-alkylene, $-CONH$-alkylene or $-CON(alkyl)$-alkylene group, wherein the alkylene moiety in each case is straight-chained and may be substituted by an alkyl, pyridyl, pyridazinyl, pyrimidinyl or pyrazinyl group or by an optionally substituted phenyl group,

(vi) R_a does not represent a hydrogen atom),

those wherein

A denotes a $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH=CH-$, $-CH_2CO-$ or $-COCH_2-$ group which may be substituted by one or two methyl groups,

a $-CH=N-$ or $-N=CH-$ group wherein the hydrogen atom may be replaced by a methyl group;

R_a denotes a hydrogen, fluorine, chlorine, bromine or iodine atom or a methyl, trifluoromethyl, methoxy or cyano group;

R_b denotes a hydrogen atom;

R_1 and R_3 independently of each other denote a hydrogen atom or an alkyl, phenyl, hydroxy, alkoxy, cyano, carboxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl or dialkylaminocarbonyl group, and

R_2, R_4, R_6 and R_8 independently of one another each denote a hydrogen atom or an alkyl group, or

R_1 together with R_2 or R_3 together with R_4 denotes an oxygen atom;

R_5 and R_7 independently of each other denote a hydrogen atom or an alkyl, phenyl, carboxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl or dialkylaminocarbonyl group;

R_9 denotes a hydrogen atom, a C_{1-6}-alkyl group, a C_{3-7}-cycloalkyl group, a cycloalkylalkyl group having 3 to 7 carbon atoms in the cycloalkyl moiety and 1 to 3 carbon atoms in the alkyl moiety, an optionally phenyl-substituted C_{3-6}-alkenyl group wherein the alkenyl group may not be connected to the nitrogen atom via the vinyl moiety, a C_{3-4}-alkynyl group, wherein the alkynyl group may not be connected to the nitrogen atom via the ethynyl moiety, a phenylalkyl or pyridylalkyl group each having 1 to 3 carbon atoms in the alkyl moiety, a

hydroxyalkyl, alkoxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, 2,2,2-trifluoroethyl, alkoxycarbonyl, phenylmethyloxycarbonyl, formyl, acetyl or trifluoroacetyl group or an alkyl group which is substituted by an amino, alkylamino, dialkylamino, cyano, alkylcarbonylamino, N-alkyl-alkylcarbonylamino, alkylsulphonylamino or N-alkyl-alkylsulphonylamino group;

D denotes an alkylene group,

a 1,4-phenylene group,

a 1,4-cyclohexylene group optionally substituted by one or two methyl groups, or

a 1,4-piperidinylene group optionally substituted by one or two methyl groups and wherein the ring nitrogen atom is linked to a carbon atom of group E;

E denotes a straight-chained alkylene group which may be substituted by an alkyl, phenyl, pyridyl, pyridazinyl, pyrimidinyl or pyrazinyl group,

a straight-chained alkylene group linked to group D via a group W, wherein W denotes an oxygen or sulphur atom or a sulphinyl, sulphonyl or $-NR_{14}-$ group, whilst the alkylene moiety may be substituted by an alkyl, phenyl, pyridyl, pyridazinyl, pyrimidinyl or pyrazinyl group and

R_{14} denotes a hydrogen atom, an alkyl group, a cycloalkyl, cycloalkyl(C_{1-3}alkyl), cycloalkylcarbonyl or cycloalkylsulphonyl group each having 3 to 7 carbon atoms in the cycloalkyl moiety, a phenyl(C_{1-3}alkyl), pyridyl(C_{1-3}-alkyl), alkylcarbonyl, alkylsulphonyl, phenylcarbonyl or phenylsulphonyl group,

or E denotes a -CONH-alkylene or -CON(alkyl)-alkylene group wherein the alkylene moiety is straight-chained and may be substituted by an alkyl, phenyl, pyridyl, pyridazinyl, pyrimidinyl or pyrazinyl group;

F denotes a carbonyl group substituted by a hydroxy group or by a C_{1-6}-alkoxy group or by a C_{5-7}-cycloalkoxy group,

wherein the shortest distance between the group F and the nitrogen atom substituted by R_9 is at least 11 bonds, and

wherein, unless otherwise stated, the above-mentioned alkyl, alkoxy and alkylene moieties may each contain 1 to 4 carbon atoms, and

each carbon atom in the above-mentioned alkylene and cycloalkylene moieties is linked to at most one heteroatom, and

the phenyl moieties of the above-mentioned groups may each be substituted by a fluorine, chlorine or bromine atom, or by a methyl, trifluoromethyl, hydroxy or methoxy group,

and the tautomers, stereoisomers and salts thereof.

Most particularly preferred compounds of the above general formula I are (with the exception of

2-[trans-4-(2-carboxyethyl)cyclohexyl]-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-4H-1,2,4-triazol-3-one,

2-[trans-4-(2-carboxyethyl)cyclohexyl]-4-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-4H-1,2,4-triazol-3-one,

1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(3-cyclopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

1-[1-(2-carboxyethyl)-4-piperidinyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

1-[1-(2-carboxyethyl)-4-piperidinyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one, and

1-[2-[(2-carboxyethyl)aminocarbonyl]ethyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

and with the proviso that at least one of the following conditions (i) to (vi) is met

(i) A denotes a $-CH_2CH_2-$, $-CH_2CO-$ or $-COCH_2-$ group substituted by one or two methyl groups, or A denotes a $-C(CH_3)=N-$ group,

(ii) at least one of the groups R_1 to R_8 does not denote a hydrogen atom,

(iii) R_9 denotes a cyclopropyl, propargyl, cinnamyl, pyridylmethyl, 2-carboxyethyl, 2-(C_{1-4}-alkoxycarbonyl)ethyl, 2-(aminocarbonyl)ethyl, 2-(methylaminocarbonyl)ethyl, 2-(dimethylaminocarbonyl)ethyl, 2-cyanoethyl, 2-methoxyethyl, 2-aminoethyl, 2-(methylamino)ethyl, 2-(dimethylamino)ethyl, 3-hydroxypropyl, 3-aminopropyl, 3-(methylamino)propyl, 3-(dimethylamino)propyl, 3-(acetylamino)propyl, 3-(methanesulphonylamino)propyl or 2,2,2-trifluoroethyl group,

(iv) D denotes a 1,4-piperidinylene group,

(v) E denotes an $-N(R_{14})-CH_2$ group wherein the $-CH_2-$ group may be substituted by a methyl, phenyl or pyridyl group, or

E denotes a $-CONHCH_2-$, $-CON(CH_3)CH_2-$, $-CONHCH_2CH_2-$ or $-CON(CH_3)CH_2CH_2-$group wherein the alkylene moiety in each case may be substituted by a methyl, phenyl or pyridyl group,

(vi) R_a denotes a fluorine or chlorine atom),

are those wherein

A denotes a $-CH_2CH_2-$, $-CH_2CO-$ or $-COCH_2-$ group which may be substituted by one or two methyl groups,

or A denotes a -CH=N- or -N=CH- group, wherein the hydrogen atom may be replaced by a methyl group;

R_a denotes a hydrogen, fluorine or chlorine atom;

R_b denotes a hydrogen atom;

R_1 and R_3 independently of each other denote a hydrogen atom or a methyl, phenyl, hydroxy, methoxy, cyano, carboxy, methoxycarbonyl, ethoxycarbonyl, aminocarbonyl, methylaminocarbonyl or dimethylaminocarbonyl group, and

R_2, R_4, R_6 and R_8 independently of each other denote a hydrogen atom or a methyl group, or

R_1 together with R_2 or R_3 together with R_4 denotes an oxygen atom;

R_5 and R_7 independently of each other denote a hydrogen atom or a methyl, phenyl, carboxy, methoxycarbonyl, ethoxycarbonyl, aminocarbonyl, methylaminocarbonyl or dimethylaminocarbonyl group;

R_9 denotes a hydrogen atom, a C_{1-4}-alkyl group, a C_{3-6}-cycloalkyl group, an allyl group optionally substituted in the 3-position by a phenyl group or by one or two methyl groups, a propargyl, 2-carboxyethyl, 2-(C_{1-4}-alkoxycarbonyl)-ethyl, 2-(aminocarbonyl)ethyl, 2-(methylaminocarbonyl)ethyl, 2-(dimethylaminocarbonyl)ethyl, 2-cyanoethyl, 2-methoxyethyl, 2-aminoethyl, 2-(methylamino)ethyl, 2-(dimethylamino)ethyl, 3-hydroxypropyl, 3-aminopropyl, 3-(methylamino)propyl, 3-(dimethylamino)propyl, 3-(acetylamino)propyl,

3-(methanesulphonylamino)propyl, 2,2,2-trifluoroethyl or pyridylmethyl group;

D denotes a methylene, ethylene or 1,4-phenylene group,

a 1,4-cyclohexylene group, or

a 1,4-piperidinylene group the ring nitrogen atom being linked to a carbon atom of group E;

E denotes a straight-chained C_{1-3}-alkylene group which may be substituted by a methyl, phenyl or pyridyl group,

a methylene group linked to the group D via a group W, wherein W is an oxygen atom or an $-NR_{14}-$ group, whilst the methylene group may be substituted by a methyl, phenyl or pyridyl group and

R_{14} denotes a hydrogen atom, a C_{1-4}-alkyl group, a cycloalkyl, cycloalkylcarbonyl or cycloalkylsulphonyl group each having 3 to 6 carbon atoms in the cycloalkyl moiety, a benzyl, alkylcarbonyl or alkylsulphonyl group each having 1 to 4 carbon atoms in the alkyl moiety, or R_{14} denotes a phenylcarbonyl or phenylsulphonyl group,

or E denotes a $-CONHCH_2-$, $-CON(CH_3)CH_2-$, $-CONHCH_2CH_2-$ or $-CON(CH_3)CH_2CH_2-$group wherein the alkylene moiety of the above-mentioned groups may be substituted in each case by a methyl, phenyl or pyridyl group; and

F denotes a carbonyl group substituted by a hydroxy group or by a C_{1-4}-alkoxy group,

whilst the shortest distance between the group F and the nitrogen substituted by R_9 is at least 11 bonds;

and the tautomers, stereoisomers and salts thereof,

particularly the compounds of the above general formula I (with the exception of

2-[trans-4-(2-carboxyethyl)cyclohexyl]-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-4H-1,2,4-triazol-3-one,

2-[trans-4-(2-carboxyethyl)cyclohexyl]-4-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-4H-1,2,4-triazol-3-one,

1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(3-cyclopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

1-[1-(2-carboxyethyl)-4-piperidinyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

1-[1-(2-carboxyethyl)-4-piperidinyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one, and

1-[2-[(2-carboxyethyl)aminocarbonyl]ethyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

and with the proviso that at least one of the following conditions (i) to (vi) is satisfied

(i) A denotes a $-CH_2CO-$ group substituted by one or two methyl groups or denotes a $-C(CH_3)=N-$ group,

(ii) R_9 denotes a cyclopropyl, cinnamyl, propargyl, 2,2,2-trifluoroethyl, 2-carboxyethyl, 2-(tert.butyloxycarbonyl)ethyl or 2-cyanoethyl group,

(iii) D denotes a 1,4-piperidinylene group,

(iv) E denotes an $-N(R_{14})-CH_2-$ group or a $-CONHCH_2CH_2-$ group wherein the ethylene moiety may be substituted by a methyl, phenyl or pyridyl group,

(v) R_1 or R_2, or R_1 and R_2 denote a methyl group,

(vi) R_a denotes a fluorine atom),

wherein:

A denotes a $-CH_2-CH_2-$ group, a $-CH_2CO$ group substituted by one or two methyl groups or denotes a $-C(CH_3)=N-$ group;

R_a denotes a hydrogen or fluorine atom;

R_b denotes a hydrogen atom;

R_1 and R_2, which may be identical or different, each denote a hydrogen atom or a methyl group;

R_3 to R_8 each denotes a hydrogen atom;

R_9 denotes a hydrogen atom or a methyl, cyclopropyl, cinnamyl, propargyl, 2,2,2-trifluoroethyl, 2-carboxyethyl, 2-(tert.butyloxycarbonyl)ethyl or 2-cyanoethyl group;

D denotes a $-CH_2-$, $-CH_2CH_2-$, 1,4-cyclohexylene group or

a 1,4-piperidinylene group wherein the ring nitrogen atom is linked to a carbon atom of group E;

E denotes a $-CH_2-$ group, an optionally methyl-substituted $-CH_2CH_2-$ group, or a $-CONHCH_2CH_2-$ group wherein the ethylene moiety may be substituted by a methyl, phenyl or pyridyl group,

or an $-NR_{14}-CH_2-$ group linked to the 1,4-cyclohexylene group of group D via the nitrogen atom, wherein

R_{14} denotes a hydrogen atom or a methyl, benzyl, acetyl or methanesulphonyl group; and

F denotes a carbonyl group substituted by a hydroxy, methoxy or ethoxy group,

whilst the shortest distance between the group F and the nitrogen atom substituted by R_9 is at least 11 bonds;

and the tautomers, stereoisomers and salts thereof.

The following may be mentioned as particularly preferred compounds:

(1) 1-[trans-4-(carboxymethylamino)cyclohexyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

(2) 1-[trans-4-(N-methyl-N-carboxymethyl-amino)cyclohexyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

(3) 1-[trans-4-(N-benzyl-N-carboxymethyl-amino)cyclohexyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

(4) 1-[trans-4-(N-methyl-N-carboxymethyl-amino)cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

(5) 1-[trans-4-(N-benzyl-N-carboxymethyl-amino)cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

(6) 1-[trans-4-(carboxymethylamino)cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one, and

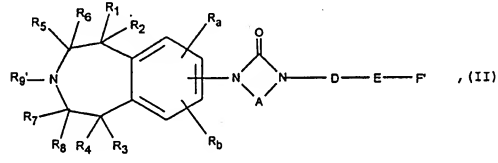
(7) 1-[trans-4-(N-acetyl-N-carboxymethyl-amino)cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

and the tautomers, stereoisomers and salts thereof.

The new compounds may be prepared, for example, by the following methods:

a) In order to prepared compounds of general formula I, wherein R_9 is as hereinbefore defined and F represents a carboxyl group or F is as hereinbefore defined and R_9 denotes a hydrogen atom:

converting a compound of general formula



, (II)

(wherein

A, D, E, R_1 to R_8, R_a and R_b are as hereinbefore defined, with the proviso that F' has the meanings given for F hereinbefore and R_9' denotes a protecting group for an imino group which can be cleaved by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis, or

R_9' has the meanings given for R_9 hereinbefore and F' denotes a group which can be converted into a carboxyl group by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis)

into a compound of general formula I wherein R_9 is as hereinbefore defined and F denotes a carboxyl group or F is as hereinbefore defined and R_9 denotes a hydrogen atom.

For example, functional derivatives of a carboxyl group such as unsubstituted or substituted amides, esters, thioesters, trimethylsilylesters, orthoesters, iminoesters, amidines or anhydrides, or a nitrile group may be converted by hydrolysis into a carboxyl group,

esters with tertiary alcohols, eg. the tert. butylester, may be converted by treatment with an acid or thermolysis into a carboxyl group, and

esters with aralkanols, eg. the benzylester, may be converted by hydrogenolysis into a carboxyl group, and

functional derivatives of an imino group, such as formyl, acetyl, trifluoroacetyl, ethoxycarbonyl, tert. butoxycarbonyl or benzyloxycarbonyl derivatives, may be converted by hydrolysis and

benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl derivatives may be converted by hydrogenolysis into the corresponding imino compounds.

The hydrolysis is appropriately carried out either in the presence of an acid such as hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, trichloroacetic acid, trifluoroacetic acid or mixtures thereof, or in the presence of a base such as lithium hydroxide, sodium hydroxide or potassium hydroxide, in a suitable solvent such as water, water/methanol, water/ethanol, water/isopropanol, methanol, ethanol, water/tetrahydrofuran or water/dioxane, at temperatures between -10 and 120°C, eg. at temperatures between ambient temperature and the boiling temperature of the reaction mixture.

Under the reaction conditions specified above, any N-acylamino or N-acylimino groups present, such as an N-trifluoroacetylimino group, may be converted into the

corresponding amino or imino groups. Furthermore, any alcoholic hydroxy groups present may be converted simultaneously into a corresponding acyloxy group, such as the trifluoroacetoxy group, during the treatment with an organic acid such as trichloroacetic acid or trifluoroacetic acid.

If F' in a compound of formula II denotes a cyano or aminocarbonyl group, these groups may also be converted into a carboxyl group with a nitrite, eg. sodium nitrite, in the presence of an acid such as sulphuric acid, which is appropriately used as solvent at the same time, at temperatures between 0 and 50°C.

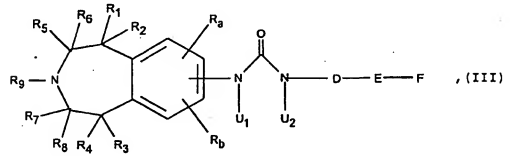
If F' and/or R_9' in a compound of formula II, for example, represents a tert. butyloxycarbonyl group, the tert. butyl group in the case of F' or the tert.butyloxycarbonyl group in the case of R_9' may also be cleaved by treatment with an acid such as trifluoroacetic acid, formic acid, p-toluenesulphonic acid, sulphuric acid, hydrochloric acid, phosphoric acid or polyphosphoric acid, optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, diethylether, tetrahydrofuran or dioxane, preferably at temperatures between -10 and 120°C, eg. at temperatures between 0 and 60°C, or by thermal treatment optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxane and preferably in the presence of a catalytic amount of an acid such as p-toluene sulphonic acid, sulphuric acid, phosphoric acid or polyphosphoric acid, preferably at the boiling temperature of the solvent used, eg. at temperatures between 40 and 120°C. Under the reaction conditions mentioned above, any N-tert. butyloxycarbonylamino or N-tert.butyloxycarbonylimino groups present may be converted into the corresponding amino or imino groups.

If F' and/or R_9' in a compound of formula II denotes, for example, a benzyloxycarbonyl group, the benzyl group in the

case of F' or the benzyloxycarbonyl group in the case of R_9' may also be hydrogenolytically cleaved in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethylacetate, dioxane or dimethylformamide, preferably at temperatures between 0 and 50°C, eg. at ambient temperature, under a hydrogen pressure of 1 to 5 bar. During hydrogenolysis, other groups may be converted at the same time, eg. a nitro group into an amino group, a benzyloxy group into a hydroxy group and an N-benzylamino, N-benzylimino, N-benzyloxycarbonylamino or N-benzyloxycarbonylimino group into a corresponding amino or imino group.

b) In order to prepare compounds of general formula I, wherein A denotes a straight-chained C_{2-3}-alkylene group which may additionally be substituted by one or two alkyl groups or by a trifluoromethyl, aryl or arylalkyl group and wherein, additionally, a methylene group in the terminal position is replaced by a carbonyl group:

cyclising a compound of general formula III optionally formed in the reaction mixture,



wherein

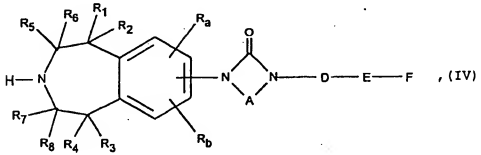
R_1 to R_9, R_a, R_b, D, E and F are as hereinbefore defined, one

of the groups U_1 or U_2 denotes a hydrogen atom and the other group U_1 or U_2 denotes a straight-chained C_{2-3}-alkylene group optionally substituted by one or two alkyl groups or by a trifluoromethyl, aryl or arylalkyl group, and wherein a terminal methylene group is replaced by a Z_1-CO- group, wherein Z_1 denotes a nucleophilically exchangeable group such as a halogen atom, a hydroxy, alkoxy, aryloxy or arylalkoxy group, e.g. a chlorine or bromine atom or a hydroxy, methoxy, ethoxy, phenoxy or benzyloxy group.

The reaction is preferably carried out in a solvent such as methylene chloride, acetonitrile, tetrahydrofuran, toluene, dimethylformamide or dimethylsulphoxide, optionally in the presence of a base such as sodium hydride, potassium carbonate, potassium-tert.butoxide or N-ethyl-diisopropylamine or optionally in the presence of a dehydrating agent such as triphenylphosphine/diethylazodicarboxylate or N,N'-carbonyldiimidazole, at temperatures between -20 and 200°C, preferably at temperatures between 0 and 160°C.

c) In order to prepare compounds of general formula I wherein R_9 denotes an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, arylalkyl or heteroarylalkyl group as mentioned in the definition of the group R_9 hereinbefore:

reacting a compound of general formula



, (IV)

(wherein
R_1 to R_8, R_a, R_b, A, D, E and F are as hereinbefore defined)
with a compound of general formula

$$Z_2 - R_{20} \qquad (V)$$

wherein
R_{20} denotes a C_{1-8}-alkyl group, a C_{3-7}-cycloalkyl group, a cycloalkylalkyl group having 3 to 7 carbon atoms in the cycloalkyl moiety and 1 to 3 carbon atoms in the alkyl moiety, an optionally aryl-substituted C_{3-6}-alkenyl group wherein the alkenyl group may not be connected to the nitrogen atom via the vinyl moiety, an optionally aryl-substituted C_{3-6}-alkynyl group, wherein the alkynyl group may not be connected to the nitrogen atom via the ethynyl moiety, an arylalkyl or heteroarylalkyl group each having 1 to 3 carbon atoms in the alkyl moiety, a hydroxyalkyl, alkoxyalkyl, 2,2,2-trifluoroethyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkylcarbonylaminoalkyl, N-alkyl-alkylcarbonylaminoalkyl, alkylsulphonylaminoalkyl, N-alkyl-alkylsulphonylaminoalkyl, cyanoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, N-alkyl-amino-carbonylalkyl or N,N-dialkyl-aminocarbonylalkyl group, wherein the aryl moiety and the alkyl moieties are as hereinbefore defined, and

Z_2 denotes a nucleophilically exchangeable group such as a halogen atom, e.g. a chlorine, bromine or iodine atom, or a sulphonic acid ester group, e.g. a methanesulphonyloxy or p-toluenesulphonyloxy group, or Z_2 together with an adjacent hydrogen atom of the group R_{20} denotes an oxygen atom).

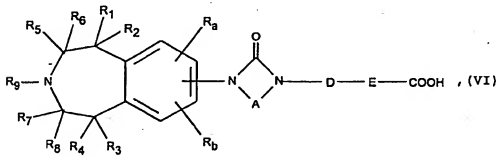
Alkylation with a compound of formula V wherein Z_2 denotes a nucleophilically exchangeable group is conveniently carried out in a solvent such as methylene chloride, tetrahydrofuran, dioxane, dimethylsulphoxide or dimethylformamide, optionally in the presence of a base such as sodium carbonate, potassium

carbonate or sodium hydroxide solution, or in the presence of a tertiary organic base such as N-ethyl-diisopropylamine or N-methylmorpholine, which may simultaneously be used as solvent, at temperatures between -30 and 150°C, but preferably at temperatures between 20 and 120°C.

The reductive alkylation with a carbonyl compound of general formula V is carried out in the presence of a complex metal hydride such as sodium borohydride, lithium borohydride or sodium cyanoborohydride, appropriately at a pH of 6-7 and at ambient temperature or in the presence of a hydrogenation catalyst, eg. with hydrogen in the presence of palladium/charcoal under a hydrogen pressure of 1 to 5 bar. The methylation is, however, preferably carried out in the presence of formic acid as the reducing agent at elevated temperatures, eg. at temperatures between 60 and 120°C.

d) In order to prepare compounds of general formula I wherein F denotes a carbonyl group which is substituted by a C_{1-6}-alkoxy group, by an arylalkoxy group or by an $R_{15}O$- group:

reacting a carboxylic acid of general formula



, (VI)

(wherein

R_1 to R_9, R_a, R_b, A, D, and E are as hereinbefore defined) or a reactive derivative thereof optionally prepared in the reaction mixture, with an alcohol of general formula

$$HO - R_{21} \qquad \text{(VII)}$$

(wherein
R_{21} denotes a C_{1-8}-alkyl group, an arylalkyl group or an R_{15} group, wherein R_{15} is a C_{4-7}-cycloalkyl group, a cycloalkylalkyl group having 3 to 7 carbon atoms in the cycloalkyl moiety, a C_{9-12}-benzocycloalkyl group or an aryl group).

Examples of reactive derivatives of a compound of general formula VI include, for example, the acid chlorides, acid azides, mixed anhydrides with aliphatic or aromatic carboxylic acid or monoesters of carbonic acid, the imidazolides thereof and the esters thereof such as the alkyl, aryl and aralkylesters, eg. the methyl, ethyl, isopropyl, pentyl, phenyl, nitrophenyl or benzylesters.

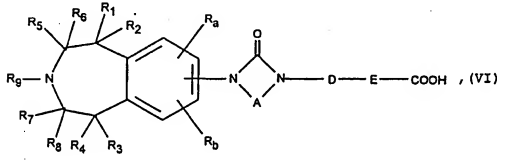
The reaction of a carboxy compound is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane or, particularly advantageously, in a corresponding alcohol of general formula VII optionally in the presence of an acid such as hydrochloric acid, or in the presence of a dehydrating agent, eg. in the presence of isobutylchloroformate, thionylchloride, trimethylchlorosilane, sulphuric acid, methanesulfonic acid, p-toluenesulfonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexyl-carbodiimide, N,N'-dicyclohexylcarbodiimide/ N-hydroxy-succinimide or 1-hydroxy-benzotriazole, and optionally also in the presence of 4-dimethylamino-pyridine, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

The reaction of a corresponding alkoxycarbonyl compound with an alcohol of general formula VII is preferably carried out in a corresponding alcohol as solvent, optionally in the presence

of another solvent such as methylene chloride or ether, preferably in the presence of an acid such as hydrochloric acid, at temperatures between 0 and 150°C, preferably at temperatures between 50 and 100°C.

e) In order to prepare compounds of general formula I, wherein F denotes an $R_{10}CO\text{-}O\text{-}(R_{11}CR_{12})\text{-}O\text{-}CO$- group:

reacting a carboxylic and of general formula



(VI)

(wherein

R_1 to R_9, R_a, R_b, A, D, and E are as hereinbefore defined) with a compound of general formula

$$Z_3 - R_{22} \qquad \text{(VIII)}$$

(wherein

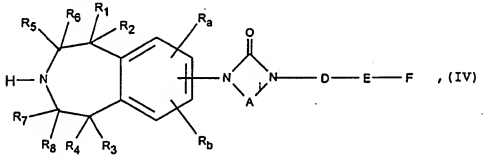
R_{22} denotes an $R_{10}CO\text{-}O\text{-}(R_{11}CR_{12})$- group, wherein R_{10} to R_{12} are as hereinbefore defined, and
Z_3 denotes a nucleophilically exchangeable group such as a halogen atom, e.g. a chlorine or bromine atom).

The reaction is preferably carried out in a solvent such as methylenechloride, tetrahydrofuran, dioxane, dimethylsulphoxide or dimethylformamide, optionally in the presence of a reaction accelerator such as sodium or potassium iodide, and preferably in the presence of a base such as

sodium carbonate, potassium carbonate or sodium hydroxide solution or in the presence of a tertiary organic base such as N-ethyl-diisopropylamine or N-methyl-morpholine, which may simultaneously serve as solvent, or optionally in the presence of silver carbonate or silver oxide, at temperatures between -30 and 100°C, but preferably at temperatures between -10 and 80°C.

f) In order to prepare compounds of general formula I, wherein R_9 denotes a C_2-alkyl group which is substituted in the 2-position by a cyano, carboxy, alkoxycarbonyl, aminocarbonyl, N-alkyl-aminocarbonyl or N,N-dialkyl-aminocarbonyl group:

reacting a compound of general formula



, (IV)

(wherein

R_1 to R_8, R_a, R_b, A, D, E and F are as hereinbefore defined)

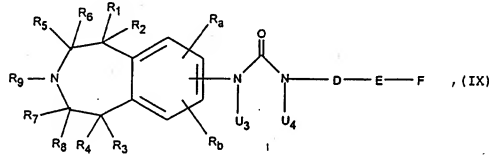
with an ethylene which is substituted by a cyano, carboxy, alkoxycarbonyl, aminocarbonyl, N-alkyl-aminocarbonyl or N,N-dialkyl-aminocarbonyl group.

The reaction is preferably carried out in a solvent such as methanol, ethanol, methylene chloride, tetrahydrofuran, toluene, dioxane, dimethylsulphoxide or dimethylformamide,

optionally in the presence of a tertiary organic base such as N-ethyl-diisopropylamine or N-methyl-morpholine, at temperatures between -30 and 150°C, but preferably at temperatures between 0 and 100°C.

g) In order to prepare compounds of general formula I, wherein A denotes a -CH=N- or -N=CH- group optionally substituted by an alkyl, trifluoromethyl, aryl or arylalkyl group:

cyclising a compound of general formula IX optionally formed in the reaction mixture



, (IX)

(wherein

R_1 to R_9, R_a, R_b, D, E and F are as hereinbefore defined,

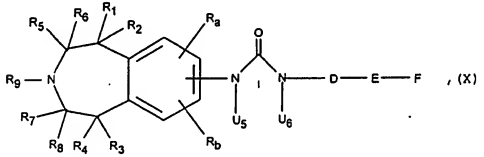
one of the groups U_3 or U_4 denotes a hydrogen atom and the other group U_3 or U_4 denotes an R_{23}-CO-NH- group, wherein R_{23} denotes a hydrogen atom or an alkyl, trifluoromethyl, aryl or aralkyl group).

The reaction is optionally carried out in a solvent such as methylene chloride, acetonitrile, tetrahydrofuran, toluene, decalin, dimethylformamide or dimethylsulphoxide, optionally in the presence of a base such as sodium hydride, potassium carbonate, potassium-tert.butoxide or N-ethyl-diisopropylamine

or optionally in the presence of an acid such as toluenesulphonic acid or optionally in the presence of dehydrating agent such as acetic anhydride or trifluoroacetic anhydride, at temperatures between 0 and 200°C, preferably at temperatures between 20 and 180°C, but most advantageously by dry heating to temperatures between 120 and 200°C.

h) In order to prepare compounds of general formula I, wherein A denotes a straight-chained C_{2-3}-alkylene group which may additionally be substituted by one or two alkyl groups or by a trifluoromethyl, aryl or arylalkyl group:

cyclising a compound of general formula X optionally formed in the reaction mixture



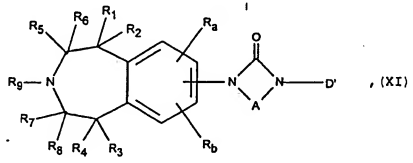
wherein

R_1 to R_9, R_a, R_b, D, E and F are as hereinbefore defined, one of the groups U_5 or U_6 denotes a hydrogen atom and the other group U_5 or U_6 denotes a straight-chained C_{2-3}-alkylene group optionally substituted by one or two alkyl groups or by a trifluoromethyl, aryl or aralkyl group, which may additionally be terminally substituted by a nucleophilically exchangeable group such as a halogen atom, a hydroxy or sulphonic acid ester group, e.g. by a chlorine, bromine or iodine atom, or by a hydroxy, methanesulphonyloxy or p-toluenesulphonyloxy group.

The reaction is preferably carried out in a solvent such as methylene chloride, acetonitrile, tetrahydrofuran, toluene, dimethylformamide or dimethylsulphoxide, optionally in the presence of a base such as sodium hydride, potassium carbonate, potassium-tert.butoxide or N-ethyl-diisopropylamine or optionally in the presence of a dehydrating agent such as triphenylphosphine/diethylazodicarboxylate, at temperatures between -20 and 100°C, preferably at temperatures between 0 and 60°C.

i) In order to prepare compounds of general formula I, wherein D denotes an optionally mono- or di-alkyl substituted C_{5-7}-cycloalkylene group, wherein a >CH- unit is replaced by a nitrogen atom and moreover in the above-mentioned 5- to 7-membered rings a methylene group adjacent to a nitrogen atom may be replaced by a carbonyl group:

alkylation of a compound of general formula



, (XI)

(wherein
R_1 to R_9, R_a, R_b and A are as hereinbefore defined and
D' denotes an optionally mono- or di-alkyl substituted C_{5-7}-cycloalkylene group wherein a >CH- unit is replaced by a nitrogen atom, the ring nitrogen atom being linked to a hydrogen atom, and moreover in the above-mentioned 5- to 7-

membered rings a methylene group adjacent to a nitrogen atom may be replaced by a carbonyl group)

with a compound of general formula

$$Z_5\text{-}E'\text{-}F \qquad (XII)$$

or with a compound of general formula

$$CH_2{=}CH\text{-}F \qquad (XIII)$$

wherein
F is as hereinbefore defined,

E' denotes a C_{1-6}-alkylene group which may be substituted by one or two C_{1-6}-alkyl groups, by a C_{2-4}-alkenyl or C_{2-4}-alkynyl group, by a hydroxy, amino, aryl or heteroaryl group, by an C_{1-6}-alkoxy or C_{1-6}-alkylamino group, by a dialkylamino group having a total of 2 to 8 carbon atoms, or by an HNR_{13}- or N-alkyl-NR_{13}- group, wherein R_{13} is as hereinbefore defined,

Z_5 denotes a nucleophilically exchangeable group such as a halogen atom, a hydroxy or sulphonic acid ester group, e.g. a chlorine, bromine or iodine atom or a hydroxy, methanesulphonyloxy or p-toluenesulphonyloxy group, and additionally the vinyl group in a compound of general formula XIII may be substituted by one or two C_{1-6}-alkyl groups, by a C_{2-4}-alkenyl or C_{2-4}-alkynyl group or by an aryl or heteroaryl group.

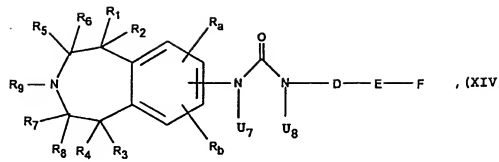
The reaction is preferably carried out in a solvent such as methanol, ethanol, methylene chloride, tetrahydrofuran, toluene, dioxane, dimethylsulphoxide or dimethylformamide optionally in the presence of an inorganic or a tertiary organic base or optionally in the presence of a dehydrating agent at temperatures between -30 and 200°C.

With a compound of general formula XII, wherein Z_5 denotes a nucleophilically exchangeable group, the reaction is preferably carried out in a solvent such as methylene chloride, acetonitrile, tetrahydrofuran, toluene, dimethylformamide or dimethylsulphoxide, optionally in the presence of a base such as sodium hydride, potassium carbonate, potassium-tert.butoxide or N-ethyl-diisopropylamine or optionally in the presence of a dehydrating agent such as triphenylphosphine/diethylazodicarboxylate, at temperatures between -20 and 100°C, preferably at temperatures between 0 and 60°C.

With a compound of general formula XIII the reaction is preferably carried out in a solvent such as methanol, ethanol, methylene chloride, tetrahydrofuran, toluene, dioxane, dimethylsulphoxide or dimethylformamide, optionally in the presence of a tertiary organic base such as N-ethyl-diisopropylamine or N-methyl-morpholine, at temperatures between -30 and 150°C, but preferably at temperatures between 0 and 100°C.

j) In order to prepare compounds of general formula I, wherein A denotes one of the straight-chained C_{2-3}-alkenylene groups mentioned hereinbefore, which may additionally be substituted by one or two alkyl groups, or by a trifluoromethyl, aryl or arylalkyl group:

cyclising a compound of general formula XIV optionally formed in the reaction mixture



, (XIV)

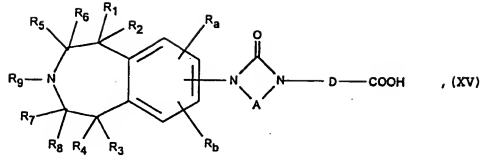
(wherein
R_1 to R_9, R_a, R_b, D, E and F are as hereinbefore defined, one of the groups U_7 or U_8 denotes a hydrogen atom and the other group U_7 or U_8 denotes a $-(CH_2)_mHC(OR_{24})_2-$ group optionally substituted in the alkylidene moiety by one or two alkyl groups or by a trifluoromethyl, aryl or aralkyl group, wherein

m denotes the number 1 or 2 and
R_{24} denotes a C_{1-4}-alkyl group).

The reaction is optionally carried out in a solvent such as methylene chloride, acetonitrile, tetrahydrofuran or toluene, preferably in the presence of an acid such as trifluoroacetic acid; acetic acid, p-toluenesulphonic acid or hydrochloric acid, at temperatures between 20 and 200°C, preferably at temperatures between 20 and 100°C.

k) In order to prepare compounds of general formula I, wherein E denotes a -CONH-alkylene, -CON(alkyl)-alkylene, -NHCO-alkylene or -N(alkyl)CO-alkylene group optionally substituted in the alkylene moiety:

reacting a compound of general formula

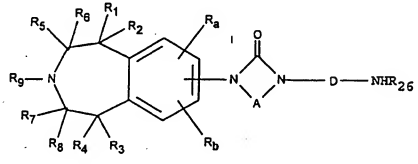


, (XV)

with an amine of general formula

$$HNR_{25} - E'' - F \qquad (XVI)$$

or reacting a amine of general formula



with a carboxylic acid of general formula

$$HOOC - E'' - F \qquad (XVIII)$$

(wherein
R_1 to R_9, R_a, R_b, A, D and F are as hereinbefore defined,
E'' denotes an alkylene group optionally substituted as mentioned hereinbefore, and
R_{25} and R_{26}, which may be identical or different, each denote a hydrogen atom or an alkyl group) or a reactive derivative

thereof).

The reaction is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane with a corresponding derivative, optionally in the presence of a tertiary organic base or in the presence of an inorganic base and/or in the presence of a dehydrating agent, e.g. in the presence of isobutylchloroformate, thionylchloride, trimethylchlorosilane, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxy-benzotriazole, N,N'-carbonyldiimidazole, triphenylphosphine/carbon tetrachloride or 2-(1H-benzotriazol-4-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate, and optionally also in the presence of 4-dimethylamino-pyridine, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

If according to the invention a compound of general formula I is obtained wherein R_{14} denotes a hydrogen atom, this may be converted by acylation or sulphonation into a corresponding compound of general formula I wherein R_{14} denotes an alkylcarbonyl, alkylsulphonyl, cycloalkylcarbonyl, cycloalkylsulphonyl, arylcarbonyl, heteroarylsulphonyl or heteroarylcarbonyl group, or

if a compound of general formula I is obtained which contains a carbon-carbon double bond, this may be converted by hydrogenation into a corresponding saturated compound.

The subsequent acylation or sulphonation is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane with a corresponding acyl or sulphonyl derivative, optionally in the

presence of a tertiary organic base or in the presence of an inorganic base or in the presence of a dehydrating agent, e.g. in the presence of isobutylchloroformate, thionylchloride, trimethylchlorosilane, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxy-benzotriazole and optionally also in the presence of 4-dimethylamino-pyridine, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, conveniently at temperatures between 0 and 150°C and preferably at temperatures between 0 and 80°C.

The subsequent hydrogenation is preferably carried out with hydrogen in the presence of a catalyst such as palladium/charcoal in a solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid, at temperatures between 0 and 100°C, but preferably at temperatures between 20 and 60°C, and under a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar.

In the reactions described hereinbefore, any reactive groups present such as hydroxy, carboxy, amino, alkylamino, imino or amidino groups may be protected during the reaction by means of conventional protecting groups which are cleaved again after the reaction.

For example, the protecting group for a hydroxy group may be a trimethylsilyl, acetyl, benzoyl, tert.butyl, trityl, benzyl or tetrahydropyranyl group,

the protecting group for a carboxyl group may be a trimethylsilyl, methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group,

the protecting group for an amidino group optionally

substituted by an alkyl group may be a benzyloxycarbonyl group and

the protecting group for an amino, alkylamino or imino group may be a formyl, acetyl, trifluoroacetyl, ethoxycarbonyl, tert.butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group, and additionally a methyl group may be used as a protecting group for an imino group and a phthalyl group may be used as a protecting group for an amino group.

The optional subsequent cleaving of a protecting group used may, for example, be carried out hydrolytically in an aqueous solution, eg. in water, isopropanol/water, acetic acid/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as sodium hydroxide or potassium hydroxide, or by ether cleavage, eg. in the presence of iodotrimethylsilane, at temperatures between 0 and 120°C, preferably at temperatures between 10 and 100°C.

However, a benzyl, methoxybenzyl or benzyloxycarbonyl group may for example be cleaved hydrogenolytically, eg. using hydrogen in the presence of a catalyst such as palladium/charcoal, in a solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid, at temperatures between 0 and 100°C, but preferably at temperatures between 20 and 60°C, under a hydrogen pressure of 1 to 7 bar, preferably 3 to 5 bar.

A tert.butyl or tert.butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid, or by treating with iodotrimethylsilane, optionally using a solvent such as methylene chloride, dioxane, methanol or ether.

A trifluoroacetyl group is preferably cleaved by treating with an acid such as hydrochloric acid, optionally in the presence of a solvent such as acetic acid or methanol, at temperatures between 50 and 120°C, or by treating with sodium hydroxide solution, optionally in the presence of a solvent such as tetrahydrofuran or methanol, at temperatures between 0 and 50°C.

A methyl group may be cleaved from a methylimino group preferably in the presence of 1-chloroalkyl choroformic acid esters such as 1-chloroethyl chloroformate, preferably in the presence of a base such as 1,8-bis-(dimethylamino)-naphthalene in the presence of a solvent such as methylene chloride, 1,2-dichloroethane, toluene or dioxane, at temperatures between 0 and 150°C, preferably at temperatures between 20°C and the boiling temperature of the reaction mixture, with subsequent treatment with an alcohol such as methanol, at temperatures between 20°C and the boiling temperature of the alcohol used.

A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine, in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxane, at temperatures between 20 and 50°C.

Furthermore, the compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers as mentioned hereinbefore. Thus, for example, cis/trans mixtures may be resolved into their cis and trans isomers, and compounds having at least one optically active carbon atom may be resolved into their enantiomers.

Thus, for example, the compounds of general formula I which occur in racemate form may be separated by methods known per se (see Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes, and compounds of general formula I having

at least 2 asymmetrical carbon atoms may be separated on the basis of their physical-chemical differences using known methods, e.g. by chromatography and/or fractional crystallisation, into the diastereomers thereof which, if they occur in racemic form, may subsequently be separated into the enantiomers as mentioned above.

The separation of enantiomers is preferably effected by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active substance (especially an acid, activated acid derivative or an alcohol thereof), which forms salts or derivatives such as esters or amides with the racemic compound, and separation of the diastereomeric salt mixture or derivative thus obtained, e.g. on the basis of their different solubilities, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Particularly common, optically active acids include, for example, the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyl tartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid or quinic acid. Examples of optically active alcohols include for example (+)- or (-)-menthol and examples of optically active acyl groups in amides include for example (+)- or (-)-menthyloxycarbonyl.

Moreover, the compounds of formula I obtained may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts thereof with inorganic or organic acids. Examples of suitable acids include hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

Furthermore, if the new compounds of formula I obtained contain a carboxyl group, they may subsequently, if desired, be converted into the salts thereof with inorganic or organic

bases, more particularly for pharmaceutical use into the physiologically acceptable salts thereof. Suitable bases for this purpose include, for example, sodium hydroxide, potassium hydroxide, arginine, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

The compounds used as starting materials are known from the literature in some cases or may be obtained by methods known from the literature (see the Examples).

As already mentioned, the new cyclic urea derivatives of general formula I and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases, have valuable properties. Thus, the new compounds of general formula I have valuable pharmacological properties, and in addition to having an inhibitory effect on inflammation and bone degradation, they have in particular antithrombotic, antiaggregatory and tumour- or metastasis-inhibiting effects.

By way of example, the compounds of general formula I were investigated for their biological effects as follows:

1. Inhibition of binding of ^{3}H-BIBU 52 to human thrombocytes:

A suspension of human thrombocytes in plasma is incubated with ^{3}H-BIBU 52 [= (3S,5S)-5-[(4'-amidino-4-biphenylyl)oxymethyl]-3-[(carboxyl)methyl]-2-pyrrolidinone[3-^{3}H-4-biphenylyl]], which replaces the ^{125}I fibrinogen ligand known from the literature (see DE-A-4214245) and various concentrations of the substance to be tested. The free and bound ligand is separated by centrifuging and quantitatively determined by scintillation counting. The inhibition of ^{3}H-BIBU 52 binding by the test substance is determined from the measurements obtained.

In order to do this, donor blood is taken from an anticubital vein and anticoagulated with trisodium citrate (final concentration 13 mM). The blood is centrifuged for 10 minutes at 170 x g and the supernatant platelet-rich plasma (PRP) is removed. The remaining blood is sharply centrifuged once more in order to obtain plasma. The PRP is diluted 1:10 with autologous plasma. 750 µl are incubated with 50 µl of physiological saline solution, 100 µl of test substance solution, 50 µl of ^{14}C-sucrose (3,700 Bq) and 50 µl of ^{3}H-BIBU 52 (final concentration: 5 nM) at ambient temperature for 20 minutes. In order to measure the non-specific binding, 5 µl of BIBU 52 (final concentration: 30 µM) are used instead of the test substance. The samples are centrifuged for 20 seconds at 10,000 x g and the supernatant is poured off. 100 µl thereof are measured in order to determine the free ligand. The pellet is dissolved in 500 µl of 0.2N NaOH, 450 µl are mixed 2 ml of scintillator and with 25 µl of 5N HCl and measured. The residual plasma remaining in the pellet is determined from the ^{14}C-content and the bound ligand is determined from the ^{3}H-measurement. After the non-specific binding has been deducted, the pellet activity is plotted against the concentration of the test substance and the concentration for a 50% inhibition of binding is determined.

2. Antithrombotic activity

Method

Thrombocyte aggregation is measured using the Born and Cross method (J. Physiol. 170: 397 (1964)) in platelet-rich plasma taken from healthy volunteers. To inhibit coagulation the blood is mixed with 3.14% sodium citrate in a volume ratio of 1:10.

Collagen-induced aggregation

The pattern of the decrease in optical density of the platelet suspension is photometrically measured and recorded after the addition of the aggregation-triggering substance. The rate of aggregation is determined from the angle of inclination of the density curve. The point on the curve where there is maximum light transmittance is used to calculate the optical density.

The amount of collagen used is as small as possible but sufficient to produce an irreversible reaction curve. Standard commercial collagen produced by Hormonchemie of Munich is used.

Before the addition of the collagen, the plasma is incubated for 10 minutes with the substance at 37°C.

From the measurements obtained an EC_{50} is determined graphically, indicating a 50% change in the optical density in terms of the inhibition of aggregation.

The table which follows contains the results found:

Substance (Example No.)	Fibrinogen-binding test IC_{50} [nM]	Inhibition of platelet aggregation EC_{50} [nM]
3	390	1200
1(3)	57	150
1(2)	150	140
9	100	160
1(6)	750	3700
3(5)	340	1000
1(18)	26	3300
1(20)	360	3700
11(11)	250	4000
11(13)	450	
15(6)	880	

On the basis of their inhibitory effect on cell-cell or cell-matrix interactions, the new cyclic urea derivatives of general formula I and the physiologically acceptable addition salts thereof are suitable for combating or preventing diseases in which smaller or greater cell aggregates occur or in which cell-matrix interactions play a part, e.g. in treating or preventing venous and arterial thrombosis, cerebrovascular diseases, lung embolism, cardiac infarction, arteriosclerosis, osteoporosis and the metastasis of tumours and the treatment of genetically caused or acquired disorders of cell interactions with one another or with solid structures. They are also suitable for parallel therapy in thrombolysis with fibrinolytics or vascular interventions such as transluminal angioplasty or in the treatment of shock, psoriasis, diabetes and inflammation.

For treating or preventing the diseases mentioned above the dosage is between 0.1 µg and 30 mg/kg bodyweight, preferably

1 µg to 15 mg/kg bodyweight, given in up to 4 doses per day. For this purpose the compounds of formula I produced according to the invention, optionally in conjunction with other active substances such as thromboxane receptor antagonists and thromboxane synthesis inhibitors or combinations thereof, serotonin antagonists, α-receptor antagonists, alkylnitrates such as glycerol trinitrate, phosphodiesterase inhibitors, prostacyclin and the analogues thereof, fibrinolytics such as tPA, prourokinase, urokinase, streptokinase, or anticoagulants such as heparin, dermatan sulphate, activated protein C, vitamin K antagonists, hirudine, inhibitors of thrombin or other activated clotting factors, may be incorporated together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, sucrose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethyleneglycol, propyleneglycol, stearylalcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, into conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions, solutions, sprays or suppositories.

The Examples which follow are intended to illustrate the invention:

Preparation of the starting materials:

Example I

N-[trans-4-[2-(Methoxycarbonyl)ethyl]cyclohexyl]-N'-[1-(methoxycarbonyl)ethyl]-N'-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-urea

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4.9 g of 7-[[1-(methoxycarbonyl)ethyl]amino]-3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine and 3.0 g of [trans-4-[2-(methoxycarbonyl)ethyl]cyclohexyl]-isocyanate (prepared from the corresponding amine-hydrochloride by reacting with phosgene) are stirred in 5 ml of dioxane for 3 days at ambient temperature and then for a further 4 hours at 70°C. The reaction mixture is concentrated by evaporation and the residue is purified by chromatography over a silica gel column with cyclohexane/ethyl acetate (65:35 and 50:50).
Yield: 5.4 g (68 % of theory),
R_f value: 0.35 (silica gel; cyclohexane/ethyl acetate = 1:1)

The following compounds are obtained analogously to Example I:

(1) N-(1-Benzyl-4-piperidinyl)-N-(2,2-dimethoxyethyl)-N'-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-urea
The (3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-benzazepin-7-yl)-isocyanate is obtained by reacting the corresponding amine with phosgene. The N-(1-benzyl-4-piperidinyl)-N-(2,2-dimethoxyethyl)-amine [R_f value: 0.64 (silica gel; toluene/dioxane/methanol/conc. aqueous ammonia = 20:50:20:10)] is obtained by reductive amination of 1-benzyl-4-piperidone with aminoacetaldehyde-dimethylacetal.
R_f value: 0.47 (silica gel; methylene chloride/acetone/conc. aqueous ammonia = 80:20:1)

(2) 1-Acetyl-2-[trans-4-[2-(methoxycarbonyl)ethyl]cyclohexyl]-4-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-semicarbazide
Reaction of 1-acetyl-2-[trans-4-[2-(methoxycarbonyl)ethyl]-cyclohexyl]hydrazine with (3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)isocyanate
Melting point: 163-165°C
R_f value: 0.38 (silica gel; cyclohexane/ethyl acetate = 1:4)

(3) N-(2,2-Diethoxyethyl)-N-(1,4-dioxaspiro[4,5]decan-8-yl)-N'-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-urea
The N-(2,2-diethoxyethyl)-N-(1,4-dioxaspiro[4,5]-decan-8-yl)-amine used [Rf value: 0.42 (silica gel; methylene chloride/methanol = 20:1)] is obtained by reductive amination of 1,4-cyclohexandione-monoethyleneketal with aminoacetaldehyde-diethylacetal.
R_f value: 0.75 (silica gel; methylene chloride/methanol = 20:1)

(4) N-(3-tert.Butyloxycarbonyl-9-fluoro-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-N'-(2,2-diethoxyethyl)-N'-[trans-4-[2-(methoxycarbonyl)ethyl]cyclohexyl]urea
Preparation of the isocyanate in situ by treating the compound of Example VI(3) with phosphoric acid diphenylester azide in the present of triethylamine.
R_f value: 0.53 (silica gel; cyclohexane/ethyl acetate = 1:1)

(5) N-(3-tert.Butyloxycarbonyl-8-fluoro-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-N'-(2,2-dimethoxyethyl)-N'-[trans-4-[2-(methoxycarbonyl)ethyl]cyclohexyl]urea

Example II

7-[[1-(Methoxycarbonyl)ethyl]amino]-3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine

To 4.59 g of 7-amino-3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine and 2.3 g of N-ethyl-diisopropylamine in 5 ml of dimethylformamide are added 2.97 g of methyl D,L-2-bromopropionate and the mixture is stirred for 18 hours at ambient temperature, 1 hour at 50°C and then a further 4 hours at 75°C. The reaction mixture is cooled, mixed with ice water and extracted with tert.butyl-methylether. The organic phase is washed with water, dilute citric acid and saline solution, dried and concentrated by evaporation. The residue is purified by chromatography over a silica gel column using cyclohexane/ethyl acetate (73:27).
Yield: 5.7 g (93 % der theory),
Melting point: 95-98°C
R_f value: 0.75 (silica gel; cyclohexane/ethyl acetate = 6:4)

The following compound is obtained analogously to Example II:

(1) 7-[[2-(ethoxycarbonyl)-2-propyl]amino]-3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine
R_f value: 0.60 (silica gel; cyclohexane/ethyl acetate = 6:4)

Example III

7-Amino-3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine

17.3 g of 7-nitro-3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine are hydrogenated in 200 ml of ethyl acetate with 3 g of 10% palladium on activated charcoal at ambient temperature under a hydrogen pressure of 50 psi for one hour. The catalyst is removed by suction filtering and the filtrate is evaporated down. The residue is heated with tert.butyl-methylether and cooled. The precipitate is suction filtered,

washed with tert.butyl-methylether and dried.
Yield: 12.2 g (79 % of theory),
Melting point: 102-104°C
R_f value: 0.31 (silica gel; cyclohexane/ethyl acetate = 2:1)

The following compounds are obtained analogously to Example III:

(1) 7-amino-3-cyclopropyl-2,3,4,5-tetrahydro-1H-3-benzazepine x 2 HCl x 0.5 H_2O
Carried out in methanol/methanolic hydrochloric acid
Melting point: 220-230°C
R_f value: 0.47 (silica gel; methylene chloride/methanol/conc. aqueous ammonia = 95:5:2)

Calc.:	C	54.94	H	7.45	N	9.85	Cl 24.95
Found:		54.64		7.56		9.69	25.12

(2) 7-amino-3,5-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-4-one
Melting point: 186-191°C

(3) 7-amino-1,1,3-trimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-2-one
Melting point: 117-121°C

(4) 8-amino-7-methoxycarbonyl-3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine
Melting point: 125-128°C
9-amino-7-methoxycarbonyl-3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine
Melting point: 201-203°C
Hydrogenation of the mixture of the corresponding nitro compounds of Example IV(2) and subsequent chromatographic separation of the isomers on silica gel using cyclohexane/methylene chloride (8:100) and methylene chloride/ethyl acetate (100:6)

Example IV

7-Nitro-3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine

To a solution of 100 g of 3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine [R_f value: 0.76 (silica gel; cyclohexane/ethyl acetate = 1:1), prepared by reacting 2,3,4,5-tetrahydro-1H-3-benzazepine with methyl trifluoroacetate] cooled to -10°C in 260 ml of conc. sulphuric acid is added, dropwise, within 2 hours, a mixture of 29.9 ml of 65% nitric acid and 10 ml of concentrated sulphuric acid at an internal temperature of -5 to -12°C. The mixture is then stirred for a further 4 hours at -10°C. The reaction mixture is poured onto ice, extracted with ethyl acetate and the combined organic phases are washed 3x with water. The organic phase is separated off, dried and evaporated down. The residue is heated to boiling with 80 ml of tert.butyl-methylether, with stirring, then cooled in an ice bath and the precipitate is suction filtered. The product obtained is washed with tert.butyl-methylether and then dried in vacuo.
Yield: 75 g (64% theory),
Melting point: 121-123°C
R_f value: 0.57 (silica gel; cyclohexane/ethyl acetate 2:1)

The following compounds are obtained analogously to Example IV:

(1) 3,4-bis-(carboxymethyl)-nitrobenzene
Melting point: 198-200°C
R_f value: 0.30 (silica gel; methylene chloride/methanol/glacial acetic acid = 95:5:2)

(2) 7-methoxycarbonyl-8-nitro-3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine and
7-methoxycarbonyl-9-nitro-3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine

R_f value: 0.28 (silica gel; cyclohexane/methylene chloride = 1:9)

The crude product obtained after nitrogenation is converted into the methylester by treating with thionylchloride and subsequently reacting with methanol in the presence of N-ethyl-diisopropylamine. The 7-carboxy-3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine used as starting material (melting point: 244-246°C) is obtained by reacting 7-carboxy-2,3,4,5-tetrahydro-1H-3-benzazepine-hydrochloride with methyl trifluoroacetate in methanol and in the presence of triethylamine.

Example V

1-(4-Piperidinyl)-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

---

10.9 g of 1-(1-benzyl-4-piperidinyl)-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-3H-imidazol-2-one are hydrogenated in 200 ml of methanol at 50°C under a hydrogen pressure of 50 psi for 14 hours in the presence of 4.5 g of palladium on charcoal. The mixture is filtered and the filtrate is evaporated down.

Yield: 8.42 g (94 % of theory),

R_f value: 0.08 (silica gel; methylene chloride/methanol/conc. aqueous ammonia = 95:5:1)

Example VI

1-(1-Benzyl-4-piperidinyl)-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-3H-imidazol-2-one

---

To 15.79 g of 1-(1-benzyl-4-piperidinyl)-3-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-3H-imidazol-2-one in 150 ml of methanol are added 9 ml of 4N sodium hydroxide solution and the mixture is heated over a steam bath for 45 minutes. The residue obtained by concentration is mixed with

100 ml of tetrahydrofuran and 7.9 g of di-tert.butylpyrocarbonate, after which 15 ml of 2N sodium hydroxide solution are added dropwise. After 30 minutes' stirring the reaction mixture is combined with tert.butylmethylether and saturated saline solution, the aqueous phase is extracted with tert.butyl-methylether and the combined organic phases are washed with saline solution. The organic phase is dried, evaporated down and the residue is purified by chromatography over a silica gel column using methylene chloride/methanol (97:3 and 95:5).
Yield: 9.6 g (60 % theory),
Melting point: 171-174°C
R_f value: 0.48 (silica gel; methylene chloride/methanol = 95:5)

The following compounds are obtained analogously to Example VI:

(1) 1-(2-carboxyethyl)-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
Melting point: 149-151°C

(2) 1-carboxymethyl-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
Rf value: 0.16 (silica gel; cyclohexane/ethyl acetate = 1:1)

(3) 7-carboxy-9-fluoro-3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepine
Rf value: 0.30 (silica gel; cyclohexane/ethyl acetate = 7:3)

(4) 7-carboxy-8-fluoro-3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepine

Example VII

1-(1-Benzyl-4-piperidinyl)-3-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-3H-imidazol-2-one

---

23.01 g of N-(1-benzyl-4-piperidinyl)-N-(2,2-dimethoxyethyl)-N'-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-urea are heated over a steam bath with 85 ml of trifluoroacetic acid for one hour. The mixture is evaporated down and the residue is distributed between ethyl acetate and aqueous sodium carbonate solution. The aqueous phase is extracted with ethyl acetate and the combined organic phases are washed with saline solution and then dried. The mixture is evaporated down, the residue is stirred with tert.butyl-methylether and the solid matter is suction filtered and dried.

Yield: 15.89 g (89 % of theory),

Melting point: 169-171°C

R_f value: 0.42 (silica gel; methylene chloride/acetone/conc. aqueous ammonia = 80:20:1)

The following compounds are obtained analogously to Example VII:

(1) 1-(4-oxocyclohexyl)-3-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-3H-imidazol-2-one

Starting material: compound of Example I(3).

Melting point. 214-216°C

R_f value: 0.34 (silica gel; cyclohexane/ethyl acetate = 1:3)

(2) 1-[trans-4-(2-methoxycarbonyl)ethyl]cyclohexyl]-3-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-3H-imidazol-2-one

Melting point: 132-134°C

R_f value: 0.35 (silica gel; methylene chloride/ethyl acetate = 85:15)

Example VIII

1-Acetyl-2-[trans-4-[2-(methoxycarbonyl)ethyl]cyclohexyl]-hydrazine

To 22.2 g of 4-[2-(methoxycarbonyl)ethyl]cyclohexanone-acetylhydrazone (melting point: 101-104°C, prepared by reacting acetylhydrazine with 4-[2-(methoxycarbonyl)ethyl]-cyclohexanone) and 7.9 g of sodium cyanoborohydride in 1.9 l of methanol are added 5.3 ml of glacial acetic acid and the mixture is stirred for 18 hours at ambient temperature. The reaction mixture is evaporated down, mixed with water, made slightly alkaline with sodium bicarbonate and extracted three times with methylene chloride. The combined organic phases are dried and evaporated down. The residue is dissolved in ethyl acetate by heating, the solution is cooled in an ice bath, the precipitate is suction filtered and washed with cold ethyl acetate. The solid matter is heated in tert.butyl-methylether then cooled, the product is suction filtered, washed with tert.butyl-methylether and then dried.
Yield: 7.0 g (31 % of theory),
Melting point: 98-100°C

The following compounds are obtained analogously to Example VIII:

(1) 1-[trans-4-(benzylamino)-cyclohexyl]-3-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
Starting materials: compound of Example IX and benzylamine, isolation of the trans-compound by chromatography over aluminium oxide.
Melting point: 205-208°C
R_f value: 0.35 (aluminium oxide; methylene chloride/methanol = 100:2)

(2) 1-[trans-4-(methylamino)-cyclohexyl]-3-(3-trifluoroacetyl-

2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
Starting material: compound of Example IX and methylamine, isolation of the trans-compound by chromatography over aluminium oxide.
Melting point: 169-171°C
R_f value: 0.19 (aluminium oxide; methylene chloride/methanol = 100:3)

Example IX

1-(4-Oxocyclohexyl)-3-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

---

12.7 g of 1-(4-hydroxycyclohexyl)-3-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one and 9.7 g of pyridinium chlorochromate are stirred in 60 ml of methylene chloride at ambient temperature for 18 hours. A further 1 g of pyridinium chlorochromate is added and stirring is continued for 3 hours. The solid matter is removed by suction filtering, the filtrate is evaporated down and the residue is purified by chromatography over a silica gel column using methylene chloride/methanol (40:1).
Yield: 7.6 g (60 % of theory),
Melting point: 80-82°C
R_f value: 0.50 (silica gel; methylene chloride/methanol = 20:1)

Example X

1-(4-Hydroxycyclohexyl)-3-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

---

23.5 g of 1-(4-oxocyclohexyl)-3-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-3H-imidazol-2-one are hydrogenated in 600 ml of methanol for 6 hours at ambient temperature in the presence of 6 g of platinum oxide under a

hydrogen pressure of 3 bar. The catalyst is removed by suction filtering, the filtrate is evaporated down and the residue is purified by chromatography over a silica gel column using methylene chloride/methanol (100:5).
Yield: 12.8 g (54 % of theory),
R_f value: 0.41 (silica gel; methylene chloride/methanol = 20:1)

The following compounds are obtained analogously to Example X:

(1) 1-[trans-4-(2-methoxycarbonyl)ethyl]cyclohexyl]-3-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
Carried out in ethyl acetate using palladium/charcoal
Melting point: 165-168°C
R_f value: 0.44 (silica gel; cyclohexane/ethyl acetate = 1:1)

(2) 1-[2-(ethoxycarbonyl)ethyl]-3-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
Carried out in ethyl acetate using palladium/activated charcoal.
Melting point: 108-110°C

(3) 1-(ethoxycarbonylmethyl)-3-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
R_f value: 0.40 (silica gel; cyclohexane/ethyl acetate = 1:1)

Example XI

Methyl 3-[trans-4-[(2,2-dimethoxyethyl)amino]cyclohexane]-propionate x 0.5 fumaric acid

---

23.8 g of methyl 3-(4-oxocyclohexane)propionate, 14.1 ml of aminoacetaldehyde-dimethylacetal and 60 g of molecule sieve (3Å) are stirred with 300 ml of toluene at ambient temperature for 18 hours. The mixture is filtered and the filtrate is

evaporated down by rotary evaporation in vacuo at 40°C. The residue is dissolved in 100 ml of methanol and 3.8 g of sodium borohydride are added thereto in batches at -25 to -30°C. The resulting mixture is stirred for 15 minutes at -25°C, for 30 minutes -10°C and then overnight at ambient temperature. It is evaporated down, water is added and the mixture is adjusted to pH 5 using hydrochloric acid. It is stirred for one hour at ambient temperature, made alkaline with potassium carbonate and extracted with ethyl acetate. The ethyl acetate extracts are dried and evaporated down.
Yield: 34.7 g (98 % of theory),
In order to carry out cis/trans-separation, 1.35 g are dissolved in 6 ml of tetrahydrofuran and 0.29 g of fumaric acid in 1 ml of tetrahydrofuran are added with stirring. The resulting mixture is stirred for one hour at ambient temperature, the solid matter is removed by suction filtering and washed with tetrahydrofuran and tert.butyl-methylether.
Yield: 0.97 g (58.5 % of theory),
The product is recrystallised from isopropanol for further purification.
Melting point: 163-164°C
R_f value: 0.52 (silica gel, treated with ammonia; ethyl acetate/methanol = 9:1)

Example XII

N-(2,2-Dimethoxyethyl)-N-[trans-4-[2-(methoxycarbonyl)ethyl]-cyclohexyl]-N'-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-urea

---

To 1.02 g of imidazole and 1.78 g of N,N'-carbonyldiimidazole in 7 ml of dimethylformamide are added dropwise, at -8°C, 2.58 g of 7-amino-3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine in 7 ml of dimethylformamide within 18 minutes. After 25 minutes' stirring at -5°C a mixture of 3.31 g of methyl 3-[trans-4-[(2,2-dimethoxyethyl)amino]cyclohexane]-

propionate x 0.5 fumaric acid, 2.77 ml of triethylamine and 15 ml of dimethylformamide are added all at once. After 18 hours' stirring at ambient temperature the mixture is poured onto 150 ml of water, stirred for 10 minutes and decanted off. The residue is taken up in ethyl acetate, washed with water, dried and evaporated down. The residue is crystallised from tert.butyl-methylether/cyclohexane.

Yield: 4.83 g (86 % of theory),

Melting point: 116-118°C

R_f value: 0.28 (silica gel; cyclohexane/ethyl acetate = 7:3)

Calc.:	C 58.16	H	6.87	N	7.54
Found:	58.28		7.00		7.65

The following compounds are obtained analogously to Example XII:

(1) N-(2-hydroxyethyl)-N-[trans-4-[2-(methoxycarbonyl)ethyl]-cyclohexyl]-N'-(3-cyclopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-urea

Melting point: 162-165°C

R_f value: 0.12 (silica gel; methylene chloride/methanol = 95:5)

(2) N-(2,2-dimethoxyethyl)-N-[trans-4-[2-(methoxycarbonyl)-ethyl]cyclohexyl]-N'-(3,5-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-urea

R_f value: 0.25 (aluminium oxide; cyclohexane/ethyl acetate = 1:1)

(3) N-(2,2-dimethoxyethyl)-N-[trans-4-[2-(methoxycarbonyl)-ethyl]cyclohexyl]-N'-(1,1,3-trimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-urea

Melting point: 103-105°C

(4) N-(2,2-dimethoxyethyl)-N-[trans-4-[2-(methoxycarbonyl)-ethyl]cyclohexyl]-N'-[3-(2,2,2-trifluoroethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-urea

R_f value: 0.40 (silica gel; cyclohexane/ethyl acetate = 3:2)

Example XIII

1-[trans-4-(2-Carboxyethyl)cyclohexyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one x HCl

---

Prepared analogously to Example 1 from the compound of Example X(1).

Melting point: >250°C

R_f value: 0.46 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C	62.62	H	7.64	N	9.98	Cl 8.40
Found:		62.24		7.67		10.01	8.86

Example XIV

1-[trans-4-[2-(Methoxycarbonyl)ethyl]cyclohexyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-hydrochloride

---

Prepared analogously to Example 4 from the compound of Example XIII.

R_f value: 0.26 (Reversed Phase silica gel; methanol/5% aqueous saline solution : 6:4)

Calc.:	C	63.36	H	7.86	N	9.64	Cl 8.13
Found:		63.34		7.88		9.73	8.11

Example XV

N-[trans-4-[2-(Methoxycarbonyl)ethyl]cyclohexyl]-ethanolamine

---

5.0 g of N-benzyl-N-[trans-4-[2-methoxycarbonyl)ethyl]cyclohexyl]-ethanolamine are hydrogenated in 150 ml of methanol with 1.0 g of 10% palladium on activated charcoal for 1 3/4 hours at 50°C under a hydrogen pressure of 50 psi. The

mixture is filtered and evaporated down.
Yield: 3.3 g (92 % of theory),
R_f value: 0.20 (silica gel; methylene chloride/methanol/conc. aqueous ammonia = 9:1:0.4)

The following compound is obtained analogously to Example XV:

(1) N-[trans-4-[2-(methoxycarbonyl)ethyl]cyclohexyl]-aminoacetaldehyde-diethylacetal
R_f value: 0.60 (aluminium oxide; cyclohexane/ethyl acetate = 3:2)

Example XVI

N-Benzyl-N-[trans-4-[2-(methoxycarbonyl)ethyl]cyclohexyl]-ethanolamine

---

6.2 g of N-[trans-4-[2-methoxycarbonyl)ethyl]cyclohexyl]-benzylamine-hydrochloride, 12.8 g of N-ethyl-diisopropylamine and 5.0 g of 2-bromoethanol are stirred for 22 hours at 100°C and then cooled. The mixture is distributed between ethyl acetate and water, the aqueous phase is extracted with ethyl acetate and the combined ethyl acetate phases are washed with saturated saline solution. The ethyl acetate phase is evaporated down and the residue is purified by chromatography over a silica gel column using methylene chloride/methanol (9:1).
Yield: 5.1 g (80 % of theory),
R_f value: 0.67 (silica gel; methylene chloride/methanol = 9:1)

The following compound is obtained analogously to Example XVI:

(1) N-benzyl-N-[trans-4-[2-(methoxycarbonyl)ethyl]cyclohexyl]-aminoacetaldehyde-diethylacetal
R_f value: 0.44 (silica gel; cyclohexane/ethyl acetate = 9:1)

Example XVII

N-[trans-4-[2-(Methoxycarbonyl)ethyl]cyclohexyl]-benzylamine-hydrochloride

---

8.0 g of methyl 3-(trans-4-aminocyclohexyl)propionate-hydrochloride, 4.3 g of benzaldehyde and 5.0 ml of triethylamine in 150 ml of methanol are hydrogenated with 1.0 g of Raney nickel at 50°C under a hydrogen pressure of 50 psi for 4 hours. After cooling the mixture is suction filtered and the filtrate is evaporated down. The residue is distributed between ethyl acetate and water, the aqueous phase is adjusted to pH 8-9 using sodium hydroxide solution and extracted with ethyl acetate. The combined ethyl acetate phases are washed with saturated saline solution, dried and evaporated down. The residue is suspended in diethylether and mixed with methanolic hydrochloric acid. The precipitate is suction filtered, washed with diethylether and dried.
Yield: 7.4 g (66 % of theory),
Melting point: 170-172°C

Calc.:	C	65.47	H	8.40	N	4.49	Cl	11.37
Found:		65.38		8.44		4.46		11.40

Example XVIII

3-Cyclopropyl-7-nitro-2,3,4,5-tetrahydro-1H-3-benzazepine-hydrochloride

---

To 20.5 g of 3,4-bis-[2-(methansulphonyloxy)ethyl]-nitrobenzene in 200 ml of dimethylformamide are added dropwise, at 70-80°C, a mixture of 3.2 g of cyclopropylamine and 15.2 g of N-ethyl-diisopropylamine within 30 minutes. The resulting mixture is then stirred for 6 hours at 90°C. The reaction mixture is poured onto 600 g of ice water mixture and extracted once more with tert.butyl-methylether. The combined extracts are washed with water and saline solution, dried and

evaporated down. The residue is dissolved in a mixture of 50 ml of acetone and 50 ml of diethylether and then combined with ethereal hydrochloric acid. After some stirring the mixture is suction filtered and the solid is washed with a little diethylether and acetone.
Yield: 4.7 g (30 % of theory),
Melting point: from 220°C (Decomp.)
R_f value of the free base: 0.65 (silica gel; methylene chloride/methanol = 95:5)

Example XIX

3,4-Bis-[2-(methanesulphonyloxy)ethyl]-nitrobenzene

To 13.6 g of 3,4-bis-(2-hydroxyethyl)-nitrobenzene (melting point: 117-119°C; prepared from 2,4-bis-(carboxymethyl)-nitrobenzene by esterification with methanol/thionylchloride and subsequent reduction with lithium borohydride in tetrahydrofuran in the presence of methanol) and 18.44 g of methanesulphonic acid chloride in 160 ml of methylene chloride are added dropwise 17.6 g of triethylamine at 0 to 10°C with stirring. After two hours stirring, ice water is added, the organic phase is separated off, washed with ice water, dried and evaporated down. The residue is purified by crystallisation with a little ethyl acetate and stirring with tert.butyl-methylether.
Yield: 20.5 g (87 % of theory),
Melting point: 91-100°C (Decomp.)
R_f value: 0.81 (silica gel; methylene chloride/methanol = 95:5)

Example XX

7-Amino-3,5-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepine

To 450 mg of 7-amino-3,5-dimethyl-2,3,4,5-tetrahydro-1H-3-

benzazepin-4-one in 10 ml of tetrahydrofuran are added, with stirring, 8.8 ml of a 1-molar borane solution in tetrahydrofuran and the mixture is then refluxed for 5 hours. A further 1 ml of the borane solution is added and the mixture is heated for a further 4 hours. It is then evaporated down, the residue is mixed with 10 ml of semiconcentrated hydrochloric acid and heated over a steam bath for 3 hours. It is evaporated down and the residue is distributed between methylene chloride and sodium hydroxide solution. The organic phase is separated off and the aqueous phase is extracted once more with methylene chloride. The combined organic phases are dried and evaporated down.
Yield: 410 mg (93 % of theory),
R_f value: 0.11 (silica gel; methylene chloride/methanol = 95:5)

The following compounds are obtained analogously to Example XX:

(1) 7-amino-1,1,3-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepine-dihydrochloride
Isolated as the hydrochloride
Melting point: 267-280°C

Calc.:	C	56.32	H	8.00	N	10.10	Cl	25.58
Found:		56.19		8.02		10.01		24.98

(2) 7-amino-3-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-3-benzazepine
Prepared from the corresponding trifluoroacetyl compound
R_f value: 0.78 (silica gel; cyclohexane/ethyl acetate = 1:1)

Example XXI

7-Nitro-1,1,3-trimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-2-one
and
3,5-Dimethyl-7-nitro-4,5-dihydro-3H-3-benzazepin-4-one

To 60 g of 3-tert.butyloxycarbonyl-7-nitro-2,3,4,5-tetrahydro-1H-3-benzazepine in 600 ml of ethyl acetate is added, with vigorous stirring, a mixture of 190 g of sodium metaperiodate and 6.2 g of ruthenium trichloride-hydrate in 800 ml of water. After 2 and 3 hours stirring a further 22 g of sodium metaperiodate in a little water are added. After another hour, the mixture is diluted with ethyl acetate and suction filtered. The aqueous phase is extracted with ethyl acetate and the combined organic phases are washed with sodium thiosulphate and saline solution, dried and concentrated by rotary evaporation. The residue is taken up in methylene chloride and mixed with 60 ml of trifluoroacetic acid, whilst cooling on ice. After stirring overnight the mixture is diluted with methylene chloride and methanol and washed until neutral with water and sodium hydrogen carbonate solution. The organic phase is evaporated down, the residue is decocted with 150 ml of ethyl acetate, the mixture is cooled with stirring and the precipitate is suction filtered.
8.0 g of this mixture (consisting of 7-nitro-2,3,4,5-tetrahydro-1H-3-benzazepin-2-one and 7-nitro-2,3,4,5-tetrahydro-1H-3-benzazepin-4-one), 120 ml of methylene chloride, 22.2 g of methyl iodide, 20.5 g of pulverised potassium hydroxide and 800 mg of dibenzo-18-crown-6 are vigorously stirred for 5 hours at ambient temperature. A further 5 ml of methyl iodide are added and the mixture is stirred for a further 16 hours. The reaction mixture is diluted with methylene chloride and water and acidified with hydrochloric acid. The organic phase is separated off, the aqueous phase is extracted with methylene chloride and the combined organic phases are washed

with sodium hydrogen sulphate solution and water, then dried and evaporated down. The residue is separated off by chromatography over silica gel using cyclohexane/ethyl acetate (1:1 to 2:8).

The following compounds are obtained:

3,5-dimethyl-7-nitro-4,5-dihydro-3H-3-benzazepin-4-one
Yield: 240 mg (2.6 % of theory),
Melting point: 192-194°C
R_f value: 0.56 (silica gel; cyclohexane/ethyl acetate = 1:1)

and

7-nitro-1,1,3-trimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-2-one
Yield: 2.4 g (25 % of theory),
Melting point: 85-89°C
R_f value: 0.44 (silica gel; cyclohexane/ethyl acetate = 1:1)

Example XXII

1-[2-(Ethoxycarbonyl)ethyl]-3-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-3H-imidazol-2-one

---

20 g of 7-[(2,2-dimethoxyethyl)amino]-3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine [R_f value: 0.59 (silica gel; cyclohexane/ethyl acetate = 3:2), prepared by reacting 7-amino-3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine with bromoacetaldehyde dimethylacetal in the presence of N-ethyl-diisopropylamine] and 8.3 g of 2-(ethoxycarbonyl)-ethylisocyanate are refluxed in 10 ml of dioxane for 3 hours. The reaction mixture is evaporated down and the residue is purified by chromatography over a silica gel column using cyclohexane/ethyl acetate (3:7).
Yield: 17.2 g (70 % of theory),

Melting point: 88-91°C

The following compound is obtained analogously to Example XXII:

(1) 1-(ethoxycarbonylmethyl)-3-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-3H-imidazol-2-one
Melting point: 105-110°C

Example XXIII

1-(2-Carboxyethyl)-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-hydrochloride

---

7.5 g of 1-[2-(ethoxycarbonyl)ethyl]-3-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one, 80 ml of tetrahydrofuran, 4.5 ml of water and 17.5 ml of 2N sodium hydroxide solution are stirred at 50°C for 3 hours. The mixture is cooled, combined with 4.8 ml of formic acid and evaporated down. The residue is combined with 16 ml of water, 6.6 ml of formic acid, 5.3 ml of 37% formalin solution and 2.95 g of sodium hydrogen carbonate are added and the resulting mixture is stirred for 18 hours at 65°C. 16 ml of 2N hydrochloric acid are added, the mixture is evaporated down, a further 16 ml of 2N hydrochloric acid are added and the mixture is evaporated down once more. The residue is stirred with ethanol, the solid matter is suction filtered and the filtrate is evaporated down. The residue is crystallised with acetone, suction filtered, washed with acetone and dried.
R_f value: 0.69 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

The following compound is obtained analogously to Example XXIII:

(1) 1-carboxymethyl-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-

benzazepin-7-yl)-imidazolidin-2-one-hydrochloride
Melting point: 273-275°C

Example XXIV

9-Fluoro-7-methoxycarbonyl-3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine

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To 2.9 g of 9-amino-7-methoxycarbonyl-3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine in 50 ml of methylene chloride are added 1.2 g of nitrosonium-tetrafluoroborate and the mixture is stirred for 30 minutes. 30 ml of 1,2-dichlorobenzene are added and then the methylene chloride is distilled off in a water bath at temperature of 110°C. The mixture is heated to 150°C for a further hour, cooled, evaporated down and the residue is purified by chromatography over a silica gel column with cyclohexane/ethyl acetate (2:8).
Yield: 2.1 g (72 % of theory),
Melting point: 100-102°C

The following compound is obtained analogously to Example XXIV:

(1) 8-fluoro-7-methoxycarbonyl-3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine

Preparation of the end products:

Example 1

3-[trans-4-(2-Carboxyethyl)cyclohexyl]-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-hydantoin-hydrochloride

---

4.7 g of 3-[trans-4-[2-(methoxycarbonyl)ethyl]cyclohexyl]-1-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-hydantoin are refluxed for 5 hours with 20 ml of glacial acetic acid and 50 ml of 3N hydrochloric acid. After standing overnight at ambient temperature the mixture is evaporated down and the residue is evaporated down several times with toluene. The residue is stirred with acetone, the solid matter is suction filtered, washed with acetone and diethylether and then dried.
Yield: 3.28 g (88 % of theory)
Melting point: >250°C
R_f value: 0.42 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C	61.39	H	7.17	N	9.34	Cl 7.88
Found:		61.48		7.20		9.37	8.03

The following compounds are obtained analogously to Example 1:

(1) 3-[trans-4-(2-carboxyethyl)cyclohexyl]-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5,5-dimethyl-hydantoin-hydrochloride x H2O
Melting point: >250°C
R_f value: 0.41 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C	59.80	H	7.53	N	8.72	Cl 7.36
Found:		59.43		7.86		8.69	7.85

(2) 1-[1-(2-carboxyethyl)-4-piperidinyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one x 2 HCl x H2O

Carried out using 3N hydrochloric acid
R_f value: 0.68 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C 53.77	H 7.38	N 11.40	Cl 14.43
Found:	53.52	7.46	10.92	14.75

(3) 1-[1-(2-carboxyethyl)-4-piperidinyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one x 2 HCl x 0.5 H2O
Melting point: >250°C
R_f value: 0.74 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C 53.85	H 7.10	N 11.96	Cl 15.14
Found:	53.76	7.10	11.75	15.79

(4) 1-(1-carboxymethyl-4-piperidinyl)-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-dihydrochloride
R_f value: 0.71 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

(5) 2-[trans-4-(2-carboxyethyl)cyclohexyl]-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-4H-1,2,4-triazol-3-one x 1.1 HCl
Melting point: >220°C
R_f value: 0.58 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C 60.24	H 7.15	N 12.77	Cl 8.89
Found:	60.33	7.16	12.92	8.63

(6) 1-[trans-4-(N-benzyl-N-carboxymethyl-amino)cyclohexyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one x 2.5 HCl x 3.5 H2O
Carried out using 2N hydrochloric acid
Rf value: 0.53 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C 53.31	H 7.27	N 8.88	Cl 14.05
Found:	53.43	7.37	8.88	14.17

(7) 1-[trans-4-(N-methyl-N-carboxymethyl-amino)cyclohexyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one x 2.6 HCl x 4 H2O

R_f value: 0.67 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C	46.57	H	7.56	N	9.87	Cl 16.25
Found:		46.43		7.55		9.79	16.21

(8) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(3-cinnamyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one x 1.1 HCl

Melting point: >250°C

R_f value: 0.08 (silica gel; methylene chloride/methanol/conc. aqueous ammonia = 90:10:2)

Calc.:	C	68.73	H	7.46	N	7.76	Cl 7.20
Found:		68.87		7.61		7.71	7.40

(9) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(3-cyclopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one x HCl

Melting point: >230°C (Decomp.)

R_f value: 0.29 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C	64.99	H	7.85	N	9.09	Cl 7.67
Found:	C	64.35		7.86		9.02	7.64

(10) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(3,5-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one x 1.2 HCl x 0.5 H2O

Melting point: 240°C (Decomp.)

R_f value: 0.34 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C	61.82	H	8.04	N	9.01	Cl 9.12
Found:	C	62.13		8.05		9.08	9.00

(11) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(3,5,5-trimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-hydrochloride

(12) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(1,1,3,5,5-pentamethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-hydrochloride

(13) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(3,4-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-hydrochloride

(14) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(2,3,4-trimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-hydrochloride

(15) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(2,2,3-trimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-hydrochloride

(16) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(3-methyl-5-oxo-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-hydrochloride

(17) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(2-carboxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-hydrochloride

(18) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(3-propargyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
Melting point: 182-185°C

Calc.:	C	70.89	H	7.85	N	9.92
Found:	C	70.64		7.82		9.87

(19) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(1,1,3-trimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-hydrochloride x H2O
Melting point: 176-180°C (Decomp.)

Calc.:	C	62.29	H	8.36	N	8.72	Cl	7.35
Found:	C	62.15		8.53		8.80		7.58

(20) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-[3-(2-carboxyethyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one-hydrochloride
Melting point: 293-299°C (Decomp.)

Calc.:	C	60.78	H	7.34	N	8.50	Cl 7.18
Found:	C	60.62		7.41		8.80	7.35

(21) 1-[trans-4-(2-methoxycarbonyl)ethyl]cyclohexyl]-3-[3-(2-carboxyethyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one-hydrochloride
Starting material: Compound of Example 5(1)
Carried out with trifluoroacetic acid, isolated as the hydrochloride
R_f value: 0.30 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C	61.47	H	7.54	N	8.27	Cl 6.98
Found:	C	61.41		7.63		8.24	6.82

(22) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-[3-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one-hydrochloride
R_f value: 0.18 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

(23) 1-[1-(1-phenyl-2-carboxyethyl)-4-piperidinyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-dihydrochloride

(24) 1-[1-[1-(3-pyridyl)-2-carboxyethyl]-4-piperidinyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-trihydrochloride
R_f value: 0.55 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)
Mass spectrum: $(M+H)^+ = 464$

(25) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-[3-(3-aminopropyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one-dihydrochloride

(26) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(9-fluoro-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-hydrochloride
R_f value: 0.44 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

(27) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(9-chloro-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-hydrochloride

(28) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(8-fluoro-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-hydrochloride

(29) 1-[trans-4-[(-carboxybenzyl)amino]cyclohexyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-dihydrochloride

(30) 1-[trans-4-[(-carboxybenzyl)amino]cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-dihydrochloride

(31) 1-[trans-4-[[(3-pyridyl)-carboxymethyl]amino]cyclohexyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-trihydrochloride

(32) 1-[trans-4-[[(3-pyridyl)-carboxymethyl]amino]cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-trihydrochloride

(33) 1-[1-(1-carboxy-2-propyl)-4-piperidinyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-dihydrochloride
R_f value: 0.65 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

(34) 1-[1-(2-carboxy-1-propyl)-4-piperidinyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-dihydrochloride

R_f value: 0.61 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Mass spectrum: $M^+ = 400$

(35) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-[3-(3-pyridyl-methyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one-dihydrochloride x 0.8 H_2O

R_f value: 0.39 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C	59.63	H	7.08	N 9.93	Cl 12.57
Found:		59.40		7.09	10.22	12.32

(36) 1-[trans-4-[(1-carboxyethyl)amino]cyclohexyl]-3-(3-methyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one-dihydrochloride

(37) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-[3-(2-methoxy-ethyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one-hydrochloride x 0.5 H_2O

R_f value: 0.33 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C	61.40	H	8.04	N 8.59	Cl 7.25
Found:		61.44		7.97	8.55	7.42

(38) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-[3-(3-hydroxy-propyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one-hydrochloride x 0.3 H_2O

Starting material: compound of Example 6(7), the ester splitting was carried out with lithium hydroxide

Melting point: 212-215°C

Calc.:	C	66.88	H	8.44	N 9.36
Found:		66.92		8.47	9.47

(39) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-[3-(2-dimethyl-

aminoethyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one-dihydrochloride
Melting point: >250°C
R_f value: 0.39 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

(40) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(6-fluoro-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-hydrochloride

Example 2

3-[trans-4-(2-Methoxycarbonyl)ethyl]cyclohexyl]-1-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-hydantoin

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To 5.0 g of N-[trans-4-[2-(methoxycarbonyl)ethyl]cyclohexyl]-N'-[1-(methoxycarbonyl)ethyl]-N'-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-urea in boiling toluene are added 60 mg of potassium-tert.butoxide and the mixture is refluxed for 20 minutes. The reaction mixture is cooled, mixed with a little glacial acetic acid and evaporated down. The residue is taken up in ethyl acetate and washed twice with saturated saline solution. The organic phase is dried and evaporated down.
Yield: 5.1 g (100 % of theory)
R_f value: 0.53 (silica gel; cyclohexane/ethyl acetate = 1:1)

The following compound is obtained analogously to Example 2:

(1) 3-[trans-4-[2-(methoxycarbonyl)ethyl]cyclohexyl]-1-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5,5-dimethyl-hydantoin
Prepared by heating 7-[[2-(ethoxycarbonyl)-2-propyl]amino]-3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine and [trans-4-[2-(methoxycarbonyl)ethyl]cyclohexyl]-isocyanate to 160-170°C for several hours.
Melting point: 131-133°C

R_f value: 0.61 (silica gel; cyclohexane/ethyl acetate = 1:1)

Example 3

3-[trans-4-(2-Carboxyethyl)cyclohexyl]-1-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-hydantoin-hydrochloride x 0.65 NaCl

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A mixture of 900 mg of 3-[trans-4-(2-carboxyethyl)cyclohexyl]-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-hydantoin-hydrochloride, 336 mg of sodium hydrogen carbonate, 490 mg of 37% formalin solution and 920 mg of formic acid in 8 ml of water are heated over a steam bath for 3 hours. The reaction mixture is evaporated down, combined with hydrochloric acid and evaporated down again. The residue is stirred with 2 ml of water and the supernatant is decanted off the residue. The residue is mixed with toluene and evaporated down and the residue is stirred with acetone. The solid matter is suction filtered, washed with acetone and dried.
Yield: 860 mg (86 % theory),
R_f value: 0.11 (silica gel; methylene chloride/methanol/conc. aqueous ammonia = 90:10:2)

Calc.:	C	57.42	H	6.63	N	8.37	Cl	11.65
Found:		56.88		6.83		8.37		11.77

The following compounds are obtained analogously to Example 3:

(1) 3-[trans-4-(2-carboxyethyl)cyclohexyl]-1-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5,5-dimethyl-hydantoin x 1.5 HCl x 0.2 H2O
R_f value: 0.40 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C	60.07	H	7.44	N	8.41	Cl	10.64
Found:		60.63		7.73		8.20		10.36

(2) 1-[1-(2-carboxyethyl)-4-piperidinyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one x 3.3 HCl x 1 NaCl x 3 H2O

R_f value: 0.73 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C	41.72	H	6.57	N	8.85	Cl 24.07
Found:		40.90		6.21		8.58	24.08

(3) 2-[trans-4-(2-carboxyethyl)cyclohexyl]-4-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-4H-1,2,4-triazol-3-one-hydrochloride

R_f value: 0.50 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

(4) 1-[trans-4-(N-benzyl-N-carboxymethyl-amino)cyclohexyl]-3-[3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one x 2.5 HCl x 2.5 H2O

Starting material: compound of Example 8; subsequent ester cleavage by heating with 2N hydrochloric acid.

R_f value: 0.56 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C	55.57	H	7.32	N	8.93	Cl 14.14
Found:		55.73		7.15		8.73	13.71

(5) 1-[trans-4-(N-methyl-N-carboxymethyl-amino)cyclohexyl]-3-[3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one x 2.7 HCl x 4.1 H2O

Starting material: compound of Example 8(1); subsequent ester cleavage by heating with 2N hydrochloric acid.

R_f value: 0.67 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C	47.07	H	7.71	N	9.55	Cl 16.31
Found:		47.02		7.81		9.53	16.28

(6) 1-[trans-4-(N-cyclopropyl-N-carboxymethyl-amino)cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-dihydrochloride

Carried out analogously to Example 3(4)

(7) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(3-methyl-5-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-imidazolidin-2-one-hydrochloride

(8) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-imidazolidin-2-one-hydrochloride

(9) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5,5-dimethyl-imidazolidin-2-one-hydrochloride

(10) 1-[trans-4-(N-butyl-N-carboxymethyl-amino)cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-dihydrochloride
Carried out analogously to Example 3(4)

(11) 1-[trans-4-(N-cyclopentyl-N-carboxymethyl-amino)cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-dihydrochloride
Carried out analogously to Example 3(4)

(12) 1-[4-(2-carboxyethyl)phenyl]-3-(3,4-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-hydrochloride

(13) 1-[1-(1-phenyl-2-carboxyethyl)-4-piperidinyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-dihydrochloride

(14) 1-[1-[1-(3-pyridyl)-2-carboxyethyl]-4-piperidinyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-trihydrochloride

(15) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-[3-(3-dimethyl-aminopropyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one-dihydrochloride

(16) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(9-fluoro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-hydrochloride

R_f value: 0.36 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

(17) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(9-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-hydrochloride

(18) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(8-fluoro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-hydrochloride

(19) 1-[1-(1-carboxy-2-propyl)-4-piperidinyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-dihydrochloride

R_f value: 0.40 (silica gel; methylene chloride/methanol/conc. aqueous ammonia = 80:20:2)

(20) 1-[1-(2-carboxy-1-propyl)-4-piperidinyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-dihydrochloride

R_f value: 0.47 (silica gel; methylene chloride/methanol/conc. aqueous ammonia = 80:20:2)

(21) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(6-fluoro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-dihydrochloride

Example 4

1-[1-[2-(Methoxycarbonyl)ethyl]-4-piperidinyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

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To 750 mg of 1-[1-[2-carboxyethyl]-4-piperidinyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one x 3.3 HCl x 1 NaCl x 3 H2O in 25 ml of methanol are added dropwise, at -40°C, 720 mg of thionylchloride. The mixture is

warmed to ambient temperature and stirred overnight. The reaction mixture is evaporated down and the residue is mixed several times with toluene and methanol and evaporated down. The residue is distributed between methylene chloride and 2N potassium carbonate solution, the organic phase is separated off, dried and evaporated down.
Yield: 450 mg (90 % of theory),
R_f value: 0.75 (silica gel; methylene chloride/methanol/conc. aqueous ammonia = 80:20:2)

The following compounds are obtained analogously to Example 4:

(1) 1-[trans-4-(methoxycarbonylmethyl-amino)cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-dihydrochloride
Carried out with thionylchloride and hydrochloric acid gas
R_f value: 0.64 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

(2) 1-[trans-4-(ethoxycarbonylmethyl-amino)cyclohexyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-dihydrochloride
Carried out with hydrochloric acid gas

(3) 1-[trans-4-(ethoxycarbonylmethyl-amino)cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-dihydrochloride
Carried out with hydrochloric acid gas

(4) 1-[trans-4-[2-(ethoxycarbonyl)ethyl]cyclohexyl]-3-(2-ethoxycarbonyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-hydrochloride
Carried out with hydrochloric acid gas

(5) 1-[1-[2-(ethoxycarbonyl)ethyl]4-piperidinyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-dihydrochloride
Carried out with hydrochloric acid gas and thionylchloride

R_f value: 0.80 (silica gel; methylene chloride/methanol/conc. aqueous ammonia = 80:20:2)

(6) 1-[1-[2-(ethoxycarbonyl)ethyl]-4-piperidinyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-dihydrohloride
Carried out with hydrochloric acid gas and thionylchloride
R_f value: 0.53 (silica gel; methylene chloride/methanol/conc. aqueous ammonia = 80:20:2)

(7) 1-[1-[2-(isobutyloxycarbonyl)ethyl]-4-piperidinyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-dihydrochloride

(8) 1-[1-[1-(3-pyridyl)-2-(ethoxycarbonyl)-ethyl]-4-piperidinyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-trihydrochloride

(9) 1-[1-[1-(3-pyridyl)-2-(ethoxycarbonyl)-ethyl]-4-piperidinyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-trihydrochloride

(10) 1-[1-[1-(methoxycarbonyl)-2-propyl]-4-piperidinyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-dihydrochloride
R_f value: 0.81 (silica gel; methylene chloride/methanol/conc. aqueous ammonia = 8:2:0.2)

Example 5

1-[1-[2-(Methoxycarbonyl)ethyl]-4-piperidinyl]-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

2.08 g of 1-(4-piperidinyl)-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one and 4.3 g of methyl acrylate are refluxed for 3 hours in 10 ml of methanol. The mixture is evaporated down and the residue is purified by chromatography over a silica gel column with

methylene chloride/methanol and then by crystallisation from methanol.
Yield: 1.8 g (72 % of theory),
Melting point: 168-170°C
R_f value: 0.40 (silica gel; methylene chloride/methanol/conc. aqueous ammonia = 95:5:2)

The following compounds are obtained analogously to Example 5:

(1) 1-[trans-4-(2-methoxycarbonyl)ethyl]cyclohexyl]-3-[3-[2-(tert.butyloxycarbonyl)ethyl]-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one
Carried out with tert.butylacrylate
R_f value: 0.18 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C 68.29	H	8.60	N	7.96
Found:	68.27		8.80		8.01

(2) 1-[trans-4-(2-methoxycarbonyl)ethyl]cyclohexyl]-3-[3-(2-cyanoethyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one
Carried out with acrylonitrile
R_f value: 0.80 (silica gel; methylene chloride/methanol = 9:1)

Calc.:	C 68.99	H	8.02	N	12.38
Found:	69.00		8.12		12.32

(3) 1-[1-[1-(methoxycarbonyl)-2-propyl]-4-piperidinyl]-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
Carried out with methyl crotonate
Melting point: 168-173°C
R_f value: 0.68 (silica gel; methylene chloride/methanol = 9:1)

(4) 1-[1-[2-(methoxycarbonyl)-1-propyl]-4-piperidinyl]-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
Carried out with methyl acrylate
Melting point: 165-167.5°C

(5) 1-[1-[1-(3-pyridyl)-2-(ethoxycarbonyl)-ethyl]-4-piperidinyl]-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
Carried out with ethyl 3-(3-pyridyl)-acrylate in ethanol in a closed vessel at 100°C
R_f value: 0.49 (silica gel; methylene chloride/methanol/conc. aqueous ammonia = 95:5:0.2)

Example 6

1-[1-(Methoxycarbonylmethyl)-4-piperidinyl]-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

2.08 g of 1-(4-piperidinyl)-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one, 1.26 g of methyl bromoacetate, 0.3 g of sodium iodide, 10 ml of acetonitrile and 1.05 g of N-ethyl-diisopropylamine are stirred for 6 hours at 60°C. The mixture is evaporated down, the residue is distributed between methylene chloride and water, the organic phase is separated off and dried. The mixture is evaporated down and the residue is purified by chromatography over a silica gel column using methylene chloride/methanol (95:5). The product is stirred with 5 ml of methanol at 0°C, the solid matter is suction filtered, washed with a little cold methanol and then dried.
Yield: 0.95 g (39 % of theory),
Melting point: 173-178°C
R_f value: 0.39 (silica gel; methylene chloride/methanol = 95:5)

The following compounds are obtained analogously to Example 6:

(1) 1-[trans-4-(N-benzyl-N-tert.butyloxycarbonylmethyl-amino)cyclohexyl]-3-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
Melting point: 168-171°C
R_f value: 0.56 (silica gel; cyclohexane/ethyl acetate = 3:2)

(2) 1-[trans-4-(N-methyl-N-tert.butyloxycarbonylmethyl-amino)-cyclohexyl]-3-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
Melting point: 151-153°C
R_f value: 0.53 (aluminium oxide; cyclohexane/ethyl acetate = 1:1)

(3) 1-[trans-4-[2-(methoxycarbonyl)ethyl]-cyclohexyl]-3-(3-cinnamyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
Starting materials: compound of Example XIV and cinnamyl chloride. Carried out at ambient temperature without the addition of sodium iodide.
R_f value: 0.34 (silica gel; methylene chloride/methanol/conc. aqueous ammonia = 95:5:1)

(4) 1-[trans-4-[2-(methoxycarbonyl)ethyl]-cyclohexyl]-3-(3-propargyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one
Melting point: 104-106°C

(5) 1-[trans-4-[2-(methoxycarbonyl)ethyl]-cyclohexyl]-3-[3-(3-pyridylmethyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one
Melting point: 144-146°C
R_f value: 0.22 (aluminium oxide; methylene chloride/ethyl acetate = 8:2)

(6) 1-[trans-4-[2-(methoxycarbonyl)ethyl]-cyclohexyl]-3-[3-(2-methoxyethyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one
Melting point: 110-112°C
R_f value: 0.42 (aluminium oxide; methylene chloride/ethyl acetate = 8:2)

(7) 1-[trans-4-[2-(methoxycarbonyl)ethyl]-cyclohexyl]-3-[3-(3-hydroxypropyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one

Melting point: 143-145°C
R_f value: 0.23 (aluminium oxide; methylene chloride/methanol = 100:1.5)

(8) 1-[trans-4-[2-(methoxycarbonyl)ethyl]-cyclohexyl]-3-[3-[2-(dimethylamino)ethyl]-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one
Melting point: sintering at 134°C
R_f value: 0.29 (aluminium oxide; methylene chloride/methanole = 100:1.5)

Example 7

2-[trans-4-[2-(Methoxycarbonyl)ethyl]cyclohexyl]-4-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-4H-1,2,4-triazol-3-one

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4.9 g of 1-acetyl-2-[trans-4-[2-(Methoxycarbonyl)ethyl]-cyclohexyl]-4-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-semicarbazide are heated to 165-175 C for 3 hours. After cooling, the residue is purified by chromatography over a silica gel column with cyclohexane/ethyl acetate (2:3).
Yield: 1.6 g (34 % of theory),
R_f value: 0.36 (silica gel; cyclohexane/ethyl acetate = 2:3)

Example 8

1-[trans-4-(N-Benzyl-N-tert.butyloxycarbonylmethyl-amino)-cyclohexyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

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To 1.9 g of 1-[trans-4-(N-benzyl-N-tert.butyloxy-carbonylmethylamino)cyclohexyl]-3-(3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one in a mixture of 20 ml of methanol and 20 ml of tetrahydrofuran are added 3 ml of 2N sodium hydroxide solution and the mixture is stirred for 2 hours at ambient temperature. 3 ml of 2N

hydrochloric acid are added and the mixture is then concentrated by evaporation. The residue is combined with water and sodium bicarbonate solution and extracted several times with ethyl acetate. The ethyl acetate phase is washed with water and saturated saline solution, dried and evaporated down.
Yield: 1.6 g (100 % of theory),
R_f value: 0.38 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

The following compound is obtained analogously to Example 8:

(1) 1-[trans-4-(N-methyl-N-tert.butyloxycarbonylmethyl-amino)-cyclohexyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
R_f value: 0.51 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Example 9

1-[trans-4-(Carboxymethylamino)cyclohexyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one x 2 HCl x 2.5 H2O

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690 mg of 1-[trans-4-(N-benzyl-N-carboxymethyl-amino)-cyclohexyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one x 2.5 HCl x 3.5 H2O are hydrogenated in 40 ml of methanol for 4 hours at ambient temperature in the presence of 500 mg of palladium on charcoal under a hydrogen pressure of 50 psi. The catalyst is filtered off and the filtrate is evaporated down. The residue is stirred with acetone, the solid matter is suction filtered, washed with acetone and dried.
Yield: 410 mg (74 % of theory),
R_f value: 0.76 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C 50.00	H 7.39	N 11.10	Cl 14.10
Found:	49.58	7.44	10.90	14.18

The following compound is obtained analogously to Example 9:

(1) 1-[trans-4-(carboxymethylamino)cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one x 2.5 HCl x 4 H2O

R_f value: 0.72 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C	46.87	H	7.59	N	9.94	Cl 15.72
Found:		46.85		7.73		10.04	15.26

Example 10

1-[trans-4-[2-(Methoxycarbonyl)ethyl]cyclohexyl]-3-(3-cyclopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

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To 0.88 g of N-(2-hydroxyethyl)-N-[trans-4-[2-(methoxycarbonyl)ethyl]cyclohexyl]-N'-(3-cyclopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-urea and 0.6 g of triphenylphosphine in 20 ml of acetonitrile are added dropwise, with stirring, at ambient temperature, 470 mg of diethyl azodicarboxylate in 5 ml of acetonitrile. After stirring overnight the mixture is evaporated down and the residue is purified by chromatography over a silica gel column using methylene chloride/methanol (99:1 to 97:3). The product is stirred with a little diethylether, suction filtered and dried.

Yield: 0.3 g (23 % of theory),

Melting point: 165-169°C

R_f value: 0.28 (silica gel; methylene chloride/methanol = 95:5)

Example 11

1-[trans-4-(N-Acetyl-N-carboxymethyl-amino)cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

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0.2 ml of 8N NaOH are added to 240 mg of 1-[trans-4-(N-acetyl-N-methoxycarbonylmethyl-amino)-cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one in 5 ml of methanol and the mixture is stirred for 2 1/2 days at ambient temperature. 0.8 ml of 2N hydrochloric acid are added and the mixture is evaporated down. The residue is stirred with acetone, the solid matter is suction filtered, washed with acetone and dried.
Yield: 290 mg (contains sodium chloride)
R_f value: 0.53 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

The following compounds are obtained analogously to Example 11:

(1) 1-[trans-4-(N-methanesulphonyl-N-carboxymethyl-amino)-cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
R_f value: 0.62 (silica gel; methanol/5% aqueous saline solution = 6:4)
Mass spectrum: (M + H)+ = 479

(2) 1-[trans-4-(N-cyclopropylcarbonyl-N-carboxymethyl-amino)-cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

(3) 1-[trans-4-(N-cyclopentylcarbonyl-N-carboxymethyl-amino)-cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

(4) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(5-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

(5) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(2-dimethylamino-carbonyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

(6) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(5-cyano-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

(7) 1-[trans-4-(N-butyryl-N-carboxymethyl-amino)cyclohexyl]-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

(8) 1-[trans-4-(N-butylsulphonyl-N-carboxymethyl-amino)-cyclohexyl]-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

(9) 1-[trans-4-(N-phenylsulphonyl-N-carboxymethyl-amino)-cyclohexyl]-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

(10) 1-[trans-4-(N-benzoyl-N-carboxymethyl-amino)cyclohexyl]-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

(11) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-[3-(2-cyanoethyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one x H_2O

R_f value: 0.52 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C	65.76	H	7.95	N 12.27
Found:		65.60		8.09	12.09

(12) 1-[2-[(2-carboxyethyl)aminocarbonyl]ethyl]-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

R_f value: 0.26 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

(13) 1-[2-[(2-carboxyethyl)aminocarbonyl]ethyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one x 2 H2O
R_f value: 0.69 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C	56.59	H	7.60	N 13.20
Found:		56.91		7.20	13.18

(14) 1-[2-[(1-carboxy-2-propyl)aminocarbonyl]ethyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
R_f value: 0.70 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)
Mass spectrum: M+ = 402

(15) 1-[2-[(1-phenyl-2-carboxyethyl)aminocarbonyl]ethyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one x 0.6 H2O
Melting point: 273-276°C

Calc.:	C	65.69	H	7.04	N 11.79
Found:		65.91		6.95	11.73

(16) 1-[2-[[1-(3-pyridyl)2-carboxyethyl]aminocarbonyl]ethyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
R_f value: 0.67 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)
Mass spectrum: M+ = 465

(17) 1-[2-[(1-carboxy-2-propyl)aminocarbonyl]ethyl]-3-(3-tert.-butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
Melting point: 123-125°C
R_f value: 0.23 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

(18) 1-[2-[(1-phenyl-2-carboxyethyl)aminocarbonyl]ethyl]-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-

7-yl)-imidazolidin-2-one
Melting point: 145-147°C
R_f value: 0.14 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

(19) 1-[2-[[1-(3-pyridyl)-2-carboxyethyl]aminocarbonyl]ethyl]-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
R_f value: 0.23 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

(20) 1-[[(2-carboxyethyl)aminocarbonyl]methyl]-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
Melting point: 155°C (Decomp.)
R_f value: 0.26 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

(21) 1-[[(1-phenyl-2-carboxyethyl)aminocarbonyl]methyl]-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
Melting point: 120-125°C

(22) 1-[[[1-(3-pyridyl)-2-carboxyethyl]aminocarbonyl]methyl]-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
R_f value: 0.15 (silica gel; methylene chloride/methanol 9:1)

(23) 1-[[(2-carboxyethyl)aminocarbonyl]methyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
R_f value: 0.63 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)
Mass spectrum: M+ = 374

(24) 1-[[(1-phenyl-2-carboxyethyl)aminocarbonyl]methyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

R_f value: 0.40 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)
Mass spectrum: M+ = 450

(25) 1-[[[1-(3-pyridyl)-2-carboxyethyl]aminocarbonyl]methyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one x 2 H2O
Melting point: 170-175°C

Calc.:	C	59.12	H	6.82	N 14.14
Found:		59.10		6.65	14.36

(26) 1-[2-[(carboxymethyl)aminocarbonyl]ethyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

(27) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-[3-[3-(acetylamino)propyl]-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one

(28) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-[3-[3-(methanesulphonylamino)propyl]-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one

(29) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-[3-[2-(aminocarbonyl)ethyl]-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one

(30) 1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-[3-[2-(dimethylaminocarbonyl)ethyl]-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one

(31) 1-[2-[N-(2-carboxyethyl)-N-methyl-aminocarbonyl]ethyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one

(32) 1-[2-[N-(1-carboxy-2-propyl)-N-methyl-aminocarbonyl]-ethyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

(33) 1-[2-[N-(1-phenyl-2-carboxy-ethyl)-N-methyl-aminocarbonyl]ethyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

(34) 1-[2-[N-[1-(3-pyridyl)-2-carboxy-ethyl]-N-methyl-aminocarbonyl]ethyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

(35) 1-[2-[N-(carboxymethyl)-N-methyl-aminocarbonyl]ethyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

(36) 1-[2-[(1-carboxyethyl)aminocarbonyl]ethyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

(37) 1-[2-[(-carboxybenzyl)aminocarbonyl]ethyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

(38) 1-[2-[[(3-pyridyl)-carboxymethyl]aminocarbonyl]ethyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

Example 12

1-[trans-4-(N-Acetyl-N-methoxycarbonylmethyl-amino)cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

---

To 300 mg of 1-[trans-4-(methoxycarbonylmethyl-amino)cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-dihydrochloride in 3 ml of methylene chloride are added 0.07 ml of acetic anhydride and 0.2 ml of triethylamine and the mixture is stirred for 3 hours at ambient temperature. The reaction mixture is combined with water and extracted three times with methylene chloride. The combined organic phases are washed with water, dried and evaporated down.

Yield: 270 mg (96 % of theory)

R_f value: 0.45 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Example 13

1-[trans-4-[2-(Methoxycarbonyl)ethyl]cyclohexyl]-3-(3,5-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-hydrochloride

---

600 mg of 1-[trans-4-[2-(methoxycarbonyl)ethyl]cyclohexyl]-3-(3,5-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-3H-imidazol-2-one in 10 ml of methanol are hydrogenated for 5 hours at 50°C under a hydrogen pressure of 50 psi in the presence of 200 mg of palladium on activated charcoal. The catalyst is filtered off and the filtrate is evaporated down. The residue is purified by chromatography over an aluminium oxide column using methylene chloride/methanol (98:2) and then converted into the hydrochloride using methanolic hydrochloric acid.
Yield: 403 mg (61 % of theory),
Melting point: 230-235°C (Decomp.)

The following compounds are obtained analogously to Example 13:

(1) 1-[trans-4-[2-(methoxycarbonyl)ethyl]cyclohexyl]-3-(1,1,3-trimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-hydrochloride
Melting point: 250°C (Decomp.)

Calc.:	C	65.32	H	8.43	N	8.79	Cl 7.42
Found:		65.00		8.56		8.63	7.46

(2) 1-[trans-4-[2-(methoxycarbonyl)ethyl]cyclohexyl]-3-[3-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-imidazolidin-2-one
Melting point: 167-170°C

Calc.: C 62.35 H 7.12 N 8.73
Found: 62.33 7.11 8.63

(3) 1-[trans-4-[2-(methoxycarbonyl)ethyl]cyclohexyl]-3-(9-fluoro-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-hydrochloride
Carried out in the presence of 1.2 equivalents of 1N hydrochloric acid
R_f value: 0.18 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

(4) 1-[trans-4-[2-(methoxycarbonyl)ethyl]cyclohexyl]-3-(8-fluoro-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-hydrochloride

Example 14

1-[trans-4-[2-(Methoxycarbonyl)ethyl]cyclohexyl]-3-(3,5-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-3H-imidazol-2-one

---

950 mg of N-(2,2-dimethoxyethyl)-N-[trans-4-[2-(methoxycarbonyl)ethyl]cyclohexyl]-N'-(3,5-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-urea are heated with 10 ml of trifluoroacetic acid over a steam bath for 7 hours. The reaction mixture is evaporated down, the residue is taken up in methylene chloride and some methanol and shaken with dilute sodium hydroxide solution and then with water. The organic phase is separated off, dried and evaporated down.
Yield: 630 mg (76 % of theory),
R_f value: 0.17 (aluminium oxide; cyclohexane/ethyl acetate = 1:1)

The following compounds are obtained analogously to Example 14:

(1) 1-[trans-4-[2-(methoxycarbonyl)ethyl]cyclohexyl]-3-(1,1,3-trimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-3H-imidazol-2-one

R_f value: 0.38 (aluminium oxide; cyclohexane/ethyl acetate = 1:1)

(2) 1-[trans-4-[2-(methoxycarbonyl)ethyl]cyclohexyl]-3-[3-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-3H-imidazol-2-one
Melting point: 132-135°C

(3) 1-[trans-4-[2-(methoxycarbonyl)ethyl]cyclohexyl]-3-(9-fluoro-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-3H-imidazol-2-one
Starting material: compound of Example I(4)
R_f value: 0.38 (aluminium oxide; cyclohexane/ethyl acetate = 100:5)

(4) 1-[trans-4-[2-(methoxycarbonyl)ethyl]cyclohexyl]-3-(8-fluoro-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-3H-imidazol-2-one

Example 15

1-[2-[(2-Carboxyethyl)aminocarbonyl]ethyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one x 3.3 trifluoroacetic acid x H2O

---

3 ml of trifluoroacetic acid are added to 310 mg of 1-[2-[(2-carboxyethyl)aminocarbonyl]ethyl]-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one in 3 ml of methylene chloride and the mixture is stirred for 2.5 hours at ambient temperature. It is evaporated down, methylene chloride is added twice and again the mixture is evaporated down and dried.
R_f value: 0.73 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C	40.00	H	4.10	N 7.29
Found:		39.95		4.13	7.29

Mass spectrum: M+ = 374

The following compounds are obtained analogously to Example 15:

(1) 1-[2-[[2-(ethoxycarbonyl)ethyl]aminocarbonyl]ethyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one x 2.5 trifluoroacetic acid x H2O

R_f value: 0.56 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C	44.25	H	4.93	N 7.94
Found:		43.91		4.84	7.63

(2) 1-[2-[[1-carboxy-2-propyl)aminocarbonyl]ethyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-trifluoroacetate

R_f value: 0.68 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Mass spectrum: M+ = 388

(3) 1-[2-[[1-(ethoxycarbonyl)-2-propyl]aminocarbonyl]ethyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-trifluoroacetate

R_f value: 0.52 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Mass spectrum: M+ = 416

(4) 1-[2-[(1-phenyl-2-carboxyethyl)aminocarbonyl]ethyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-trifluoroacetate

R_f value: 0.58 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Mass spectrum: M+ = 450

(5) 1-[2-[[1-phenyl-2-(ethoxycarbonyl)-ethyl]aminocarbonyl]-ethyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one x 3.5 trifluoroacetic acid x 1.5 H2O

R_f value: 0.41 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C	45.54	H	4.55	N 6.25
Found:		45.45		4.50	6.17

(6) 1-[2-[[1-(3-pyridyl)-2-carboxyethyl]aminocarbonyl]ethyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-trifluoroacetate

R_f value: 0.71 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

(7) 1-[2-[[1-(3-pyridyl)-2-(ethoxycarbonyl)-ethyl]aminocarbonyl]ethyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-trifluoroacetate

R_f value: 0.59 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Mass spectrum: M+ = 479

(8) 1-[[(2-carboxyethyl)aminocarbonyl]methyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-trifluoroacetate

R_f value: 0.76 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Mass spectrum: M+ = 360

(9) 1-[[(1-phenyl-2-carboxyethyl)aminocarbonyl]methyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-trifluoroacetate

R_f value: 0.43 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Mass spectrum: M+ = 436

(10) 1-[[[1-phenyl-2-(ethoxycarbonyl)-ethyl]aminocarbonyl]-methyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one x 2 trifluoroacetic acid x 0.5 H_2O

R_f value: 0.25 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

Calc.:	C 51.36	H	5.03	N	7.98
Found:	51.10		5.06		7.71

(11) 1-[[[1-(3-pyridyl)-2-carboxyethyl]aminocarbonyl]methyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-trifluoroacetate
R_f value: 0.63 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

(12) 1-[[[1-(3-pyridyl)-2-(ethoxycarbonyl)-ethyl]-aminocarbonyl]methyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-trifluoroacetate
R_f value: 0.65 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)
Mass spectrum: M+ = 465

(13) 1-[2-[(carboxymethyl)aminocarbonyl]ethyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one-trifluoroacetate

Example 16

1-[2-[[2-(Ethoxycarbonyl)ethyl]aminocarbonyl]ethyl]-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

---

2.1 ml of triethylamine are added to 1.0 g of 1-(2-carboxyethyl)-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one, 410 mg of ß-alanine ethylester-hydrochloride and 860 mg of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate in 25 ml of dimethylformamide and the mixture is stirred for 18 hours at ambient temperature. The reaction mixture is combined with 150 ml of water, the precipitate is suction filtered, washed with water and dried at 60°C.
Yield: 870 mg (70 % of theory),
Melting point: 86-89°C
R_f value: 0.73 (silica gel; methylene chloride/methanol = 9:1)

The following compounds are obtained analogously to Example 16:

(1) 1-[2-[[2-(ethoxycarbonyl)ethyl]aminocarbonyl]ethyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
R_f value: 0.57 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

(2) 1-[2-[[1-(ethoxycarbonyl)-2-propyl]aminocarbonyl]ethyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one x 0.5 H2O
Melting point: 87-90°C

Calc.:	C	62.85	H	8.03	N 12.75
Found:		62.93		8.10	12.54

(3) 1-[2-[[1-phenyl-2-(ethoxycarbonyl)-ethyl]aminocarbonyl]-ethyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
R_f value: 0.40 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

(4) 1-[2-[[1-(3-pyridyl)-2-(ethoxycarbonyl)-ethyl]aminocarbonyl]ethyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
R_f value: 0.57 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)
Mass spectrum: M+ = 493

(5) 1-[2-[[1-(ethoxycarbonyl)-2-propyl]aminocarbonyl]ethyl]-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
Melting point: 93-96°C
R_f value: 0.73 (silica gel; methylene chloride/methanol = 9:1)

(6) 1-[2-[[1-phenyl-2-(ethoxycarbonyl)-ethyl]aminocarbonyl]-ethyl]-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
R_f value: 0.81 (silica gel; methylene chloride/methanol = 3:1)

(7) 1-[2-[[1-(3-pyridyl)-2-(ethoxycarbonyl)-ethyl]aminocarbonyl]ethyl]-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
R_f value: 0.10 (Reversed Phase silica gel; methanol/5% aqueous saline solution = 6:4)

(8) 1-[[[2-(ethoxycarbonyl)ethyl]aminocarbonyl]methyl]-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
Melting point: 135-137°C

(9) 1-[[[1-phenyl-2-(ethoxycarbonyl)-ethyl]aminocarbonyl]-methyl]-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
Melting point: 122-124°C

(10) 1-[[[1-(3-pyridyl)-2-(ethoxycarbonyl)-ethyl]aminocarbonyl]methyl]-3-(3-tert.butyloxycarbonyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
Melting point: 138-141°C

(11) 1-[[[2-(ethoxycarbonyl)ethyl]aminocarbonyl]methyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
Melting point: 116-118°C
Mass spectrum: M+ = 402

(12) 1-[[[1-phenyl-2-(ethoxycarbonyl)-ethyl]aminocarbonyl]-methyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one
R_f value: 0.57 (silica gel; methylene chloride/methanol/conc. aqueous ammonia = 4:1:0.1)
Mass spectrum: M+ = 478

(13) 1-[[[1-(3-pyridyl)-2-(ethoxycarbonyl)-ethyl]aminocarbonyl]methyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one x 0.5 H2O
R_f value: 0.62 (silica gel; methylene chloride/methanol/conc.

aqueous ammonia = 4:1:0.1)

Calc.:	C	63.91	H	7.01	N 14.33
Found:		63.88		7.05	13.97

Example 17

Dry ampoule containing 2.5 mg of active substance per 1 ml

Composition:

Active substance	2.5 mg
Mannitol	50.0 mg
Water for injections ad	1.0 ml

Preparation:

The active substance and mannitol are dissolved in water. After transferring the solution to the ampoule, it is freeze-dried.

At the point of use, the solution is made up with water for injections.

Example 18

Dry ampoule containing 35 mg of active substance per 2 ml

Composition:

Active substance	35.0 mg
Mannitol	100.0 mg
Water for injections ad	2.0 ml

Preparation:

The active substance and mannitol are dissolved in water. After transferring the solution to the ampoule, it is freeze-dried.

At the point of use, the solution is made up with water for injections.

Example 19

Tablet containing 50 mg of active substance

Composition:

(1) Active substance	50.0 mg
(2) Lactose	98.0 mg
(3) Corn starch	50.0 mg
(4) Polyvinylpyrrolidone	15.0 mg
(5) Magnesium stearate	2.0 mg
	215.0 mg

Preparation:

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granules. From this mixture, compressed tablets are produced. They are biplanar, facetted on both sides and notched on one side. Diameter of tablets: 9 mm.

Example 20

Tablet containing 350 mg of active substance

Composition:

(1) Active substance	350.0 mg
(2) Lactose	136.0 mg
(3) Corn starch	80.0 mg
(4) Polyvinylpyrrolidone	30.0 mg

(5) Magnesium stearate	4.0 mg
	600.0 mg

Preparation:

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granules. From this mixture, compressed tablets are produced. They are biplanar, facetted on both sides and notched on one side. Diameter of tablets: 12 mm.

Example 21

Capsules containing 50 mg of active substance

Composition:

(1) Active substance	50.0 mg
(2) Dried corn starch	58.0 mg
(3) Powdered lactose	50.0 mg
(4) Magnesium stearate	2.0 mg
	160.0 mg

Preparation:

(1) is triturated with (3). This triturate is added to the mixture of (2) and (4), with thorough mixing.

This powder mixture is packed into size 3 hard gelatin oblong capsules in a capsule filling machine.

Example 22

Capsules containing 350 mg of active substance

Composition:

(1) Active substance	350.0 mg
(2) Dried corn starch	46.0 mg
(3) Powdered lactose	30.0 mg
(4) Magnesium stearate	4.0 mg
	430.0 mg

Preparation:

(1) is triturated with (3). This triturate is added to the mixture of (2) and (4), with thorough mixing.

This powder mixture is packed into size 0 hard gelatin oblong capsules in a capsule filling machine.

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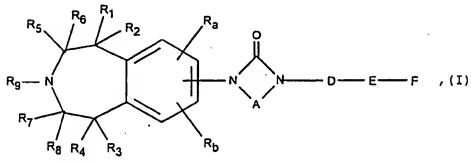
Patent Claims

1. Cyclic urea derivatives of general formula



(wherein (with the proviso that at least one of the following conditions (i) to (vi) is satisfied,

i) A denotes a mono- or di-alkyl substituted straight-chained C_{2-3}-alkylene group wherein a methylene group is optionally replaced by a carbonyl group, or A denotes a -CH=N- group in which the hydrogen atom is replaced by an alkyl group,

ii) at least one of the groups R_1 to R_8 does not represent a hydrogen atom,

iii) R_9 denotes a cyclopropyl group, a C_{3-6}-alkenyl group substituted by an aryl group or a C_{3-6}-alkynyl group optionally substituted by an aryl group, or R_9 denotes a heteroarylalkyl group having 1 to 3 carbon atoms in the alkyl moiety, a 2,2,2-trifluoroethyl group, an alkyl group which is substituted by an alkoxy, cyano, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, amino, alkylamino, dialkylamino, alkylcarbonylamino, N-alkyl-alkylcarbonylamino, alkylsulphonylamino or N-alkyl-alkylsulphonylamino group, or R_9 denotes a C_{2-4}-alkyl group substituted by a carboxy or

alkoxycarbonyl group, or a R_9 denotes C_{3-4}-alkyl group substituted by a hydroxy group,

iv) D denotes an optionally mono- or di-alkyl substituted C_{5-7}-cycloalkylene group wherein a >CH- unit is replaced by a nitrogen atom and wherein additionally in the above-mentioned 5- to 7-membered rings a methylene group adjacent to a nitrogen atom is optionally replaced by a carbonyl group,

v) E denotes a -CONH-alkylene, -CON(alkyl)-alkylene, -NHCO-alkylene or -N(alkyl)CO-alkylene group wherein the alkylene moiety of the above-mentioned groups is optionally substituted by one or two alkyl groups or by an aryl or heteroaryl group, or E denotes an $-N(R_{14})$-alkylene group, wherein the alkylene moiety may additionally be substituted by one or two C_{1-6}-alkyl groups, by a C_{2-4}-alkenyl or C_{2-4}-alkynyl group, by a hydroxy, amino, aryl or heteroaryl group, by a C_{1-6}-alkoxy or C_{1-6}-alkylamino group, by a dialkylamino group having a total of 2 to 8 carbon atoms, or by an HNR_{13} or N-alkyl-NR_{13} group, and

vi) R_8 does not denote a hydrogen atom):

A denotes a straight-chained C_{2-3}-alkylene or C_{2-3}-alkenylene group which may be additionally substituted by one or two alkyl group or by a trifluoromethyl, aryl or arylalkyl group and wherein, additionally, a methylene group may be replaced by a carbonyl group,

a C_{5-7}-1,2-cycloalkylene or C_{5-7}-1,2-cycloalkenylene group which may be substituted by one or two alkyl groups,

a 1,2-arylene group,

a -CO-NH- or -NH-CO- group wherein the hydrogen in each case may be replaced by an alkyl, aryl or arylalkyl group, or a -CH=N- or -N=CH- group wherein the hydrogen atom in each case

may be replaced by an alkyl, trifluoromethyl, aryl or arylalkyl group,

R_a and R_b, which may be identical or different, denote a hydrogen, fluorine, chlorine, brome or iodine atom or an alkyl, trifluoromethyl, alkoxy or cyano group;

R_1 and R_3 independently of each other denote a hydrogen atom or an alkyl, aryl, hydroxy, alkoxy, cyano, carboxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl or dialkylaminocarbonyl group, and

R_2, R_4, R_6 and R_8 independently of one another each denote a hydrogen atom or an alkyl group, or

R_1 together with R_2 or R_3 together with R_4 denotes an oxygen atom;

R_5 and R_7 independently of each other denote a hydrogen atom or an alkyl, aryl, carboxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl or dialkylaminocarbonyl group;

R_9 denotes a hydrogen atom, a C_{1-6}-alkyl group, a C_{3-7}-cycloalkyl group, a cycloalkylalkyl group having 3 to 7 carbon atoms in the cycloalkyl moiety and 1 to 3 carbon atoms in the alkyl moiety, an optionally aryl-substituted C_{3-6}-alkenyl group, wherein the alkenyl group may not be connected to the nitrogen atom via the vinyl moiety, an optionally aryl-substituted C_{3-6}-alkynyl group in which the alkynyl group may not be connected to the nitrogen atom via the ethynyl moiety, an arylalkyl or heteroarylalkyl group each having 1 to 3 carbon atoms in the alkyl moiety, a hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkylcarbonylaminoalkyl, N-alkyl-alkylcarbonylaminoalkyl, alkylsulphonylaminoalkyl, N-alkyl-alkylsulphonylaminoalkyl, cyanoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, N-alkyl-aminocarbonylalkyl, N,N-dialkyl-aminocarbonylalkyl,

alkoxycarbonyl, arylmethyloxycarbonyl, formyl, acetyl, trifluoroacetyl, 2,2,2-trifluoroethyl, or amidino group or a $R_{10}CO\text{-}O\text{-}(R_{11}CR_{12})\text{-}O\text{-}CO\text{-}$ group, wherein

R_{10} denotes a C_{1-8}-alkyl group, a C_{5-7}-cycloalkyl group, an aryl group or arylalkyl group having 1 to 3 carbon atoms in the alkyl moiety,

R_{11} denotes a hydrogen atom, an alkyl group, a C_{5-7}-cycloalkyl group or an aryl group, and

R_{12} denotes a hydrogen atom or an alkyl group;

D denotes an alkylene group,

an arylene group,

a C_{4-7}-cycloalkylene group optionally substituted by one or two alkyl groups,

or an optionally mono- or di-alkyl substituted C_{5-7}-cycloalkylene group wherein a >CH- unit is replaced by a nitrogen atom, the ring nitrogen atom being linked to a carbon atom of group E, and moreover in the above-mentioned 5- to 7-membered rings a methylene group adjacent to a nitrogen atom may be replaced by a carbonyl group;

E denotes a C_{1-6}-alkylene group which may be substituted by one or two C_{1-6}-alkyl groups, by a C_{2-4}-alkenyl- or C_{2-4}-alkynyl group, by a hydroxy, amino, aryl or heteroaryl group, by a C_{1-6}-alkoxy or C_{1-6}-alkylamino group, by a dialkylamino group having a total of 2 to 8 carbon atoms, or by an HNR_{13}- or N-alkyl-NR_{13}- group, wherein

R_{13} denotes an alkylcarbonyl or alkylsulphonyl group each having 1 to 6 carbon atoms in the alkyl moiety, an alkyloxycarbonyl group having a total of 2 to 5 carbon

atoms, a cycloalkylcarbonyl or cycloalkylsulphonyl group each having 5 to 7 carbon atoms in the cycloalkyl moiety, an arylalkylcarbonyl, arylalkylsulphonyl, arylalkoxycarbonyl, arylcarbonyl or arylsulphonyl group,

or E denotes an alkylene group linked to the group D via a group W, (wherein W denotes an oxygen or sulphur atom, or a sulphinyl-, sulphonyl- or -NR_{14}- group, wherein

R_{14} denotes a hydrogen atom, an alkyl group, a cycloalkyl, cycloalkylalkyl, cycloalkylcarbonyl or cycloalkylsulphonyl group each having 3 to 7 carbon atoms in the cycloalkyl moiety, or an aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkylcarbonyl, alkylsulphonyl, arylcarbonyl, heteroarylcarbonyl, arylsulphonyl, or heteroarylsulphonyl group)

and the alkylene group may additionally be substituted by one or two C_{1-6}-alkyl groups, by an alkenyl or alkynyl group each having 2 to 4 carbon atoms, by a hydroxy, amino, aryl or heteroaryl group, by an alkoxy or alkylamino group each having 1 to 6 carbon atoms, by a dialkylamino group having a total of 2 to 8 carbon atoms, or by an HNR_{13}- or N-alkyl-NR_{13}- group, wherein the heteroatom of the additional substituent is separated from a heteroatom of the group W by at least 2 carbon atoms and R_{13} is as hereinbefore defined,

or E denotes a -CONH-alkylene, -CON(alkyl)-alkylene, -NHCO-alkylene or -N(alkyl)CO-alkylene group, wherein the alkylene moiety of the above-mentioned groups may be substituted in each case by one or two alkyl groups or by an aryl or heteroaryl group; and

F denotes a carbonyl group substituted by a hydroxy group, by a C_{1-9}-alkoxy group, by an arylalkoxy group or by an $R_{15}O$- group, wherein

R_{15} denotes a C_{4-7}-cycloalkyl group or a cycloalkylalkyl group having 3 to 7 carbon atoms in the cycloalkyl moiety, a C_{9-12}-benzocycloalkyl group or an aryl group,

or F denotes an $R_{16}CO\text{-}O\text{-}CHR_{17}\text{-}O\text{-}CO$ group, wherein

R_{16} denotes a C_{1-6}-alkyl or C_{1-6}-alkoxy group, a cycloalkyl or cycloalkyloxy group each having 5 to 7 carbon atoms in the cycloalkyl moiety, an aryl, aryloxy, arylalkyl or arylalkoxy group, and

R_{17} denotes a hydrogen atom or an alkyl group,

and the shortest distance between the group F and the nitrogen atom substituted by R_9 is at least 11 bonds;

whilst, unless otherwise specified,

any aryl moiety mentioned in the definition of the above-mentioned groups may be a phenyl group which may be monosubstituted by R_{18}, mono-, di- or trisubstituted by R_{19}, or monosubstituted by R_{18} and additionally mono- or disubstituted by R_{19}, wherein the substituents may be identical or different and

R_{18} denotes a cyano, carboxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonyl, alkylcarbonyl, alkylsulphenyl, alkylsulphinyl, alkylsulphonyl, alkylsulphonyloxy, perfluoroalkyl, perfluoroalkoxy, nitro, amino, alkylamino, dialkylamino, alkylcarbonylamino, phenylalkylcarbonylamino, phenylcarbonylamino, alkylsulphonylamino, phenylalkylsulphonylamino, phenylsulphonylamino, N-alkyl-alkylcarbonylamino, N-alkyl-phenylalkylcarbonyl-amino, N-alkyl-phenylcarbonylamino, N-alkyl-alkyl-sulphonylamino, N-alkyl-phenylalkylsulphonylamino, N-alkyl-phenylsulphonylamino, aminosulphonyl,

alkylaminosulphonyl or dialkylaminosulphonyl group, and

R_{19} denotes an alkyl, hydroxy or alkoxy group, or a fluorine, chlorine, bromine or iodine atom, whilst two groups R_{19}, provided that they are bound to adjacent carbon atoms, may also denote a C_{3-5}-alkylene group, a 1,3-butadiene-1,4-diylene group or a methylenedioxy group,

any arylene moiety mentioned in the definition of the above groups may be a phenylene group which may be monosubstituted by R_{18}, mono- or disubstituted by R_{19}, or monosubstituted by R_{18} and additionally monosubstituted by R_{19}, wherein the substituents may be identical or different and are defined as hereinbefore,

any heteroaryl moiety mentioned in the definition of the above groups may be a 5-membered heteroaromatic ring which contains an oxygen, sulphur or nitrogen atom, a nitrogen and an oxygen, sulphur or nitrogen atom, or two nitrogen atoms and an oxygen, sulphur or nitrogen atom, or a 6-membered heteroaromatic ring which contains 1, 2 or 3 nitrogen atoms and wherein additionally one or two -CH=N- groups may each be replaced by a -CO-NH- group, wherein

the above-mentioned heteroaromatic rings may be substituted by one or two alkyl groups or, on the carbon skeleton, by a fluorine, chlorine, bromine or iodine atom, or by a hydroxy or alkoxy group,

and unless otherwise specified the above-mentioned alkyl, alkylene or alkoxy moieties may each contain 1 to 4 carbon atoms, and each carbon atom in the above-mentioned alkylene and cycloalkylene moieties is linked to at most one heteroatom)

and the tautomers, stereoisomers and salts thereof.

2. Cyclic urea derivatives of general formula I according to claim 1 wherein (with the exception of

2-[trans-4-(2-carboxyethyl)cyclohexyl]-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-4H-1,2,4-triazol-3-one,

2-[trans-4-(2-carboxyethyl)cyclohexyl]-4-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-4H-1,2,4-triazol-3-one,

1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(3-cyclopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

1-[1-(2-carboxyethyl)-4-piperidinyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

1-[1-(2-carboxyethyl)-4-piperidinyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one, and

1-[2-[(2-carboxyethyl)aminocarbonyl]ethyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

and with the proviso that at least one of the following conditions (i) to (vi) is satisfied

i) A denotes a mono- or di-alkyl substituted straight-chained C_{2-3}-alkylene group in which a methylene group may be replaced by a carbonyl group, or denotes a -CH=N- group in which the hydrogen atom is replaced by an alkyl group,

ii) at least one of the groups R_1 to R_8 does not represent a hydrogen atom,

iii) R_9 denotes a cyclopropyl group, a C_{3-6}-alkenyl group substituted by an aryl group, or a C_{3-6}-alkynyl group optionally substituted by an aryl group, or a heteroarylalkyl group having 1 to 3 carbon atoms in the alkyl moiety, a 2,2,2-trifluoroethyl group, an alkyl group which is substituted by an alkoxy, cyano, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, amino, alkylamino, dialkylamino,

alkylcarbonylamino, N-alkyl-alkylcarbonylamino, alkylsulphonylamino or N-alkyl-alkylsulphonylamino group, or R_9 denotes a C_{2-4}-alkyl group substituted by a carboxy or alkoxycarbonyl group, or denotes a C_{3-4}-alkyl group substituted by a hydroxy group,

iv) D denotes an optionally mono- or di-alkyl substituted C_{5-7}-cycloalkylene group wherein a >CH- unit is replaced by a nitrogen atom and wherein additionally in the above-mentioned 5- to 7-membered rings a methylene group adjacent to a nitrogen atom may be replaced by a carbonyl group,

v) E denotes a -CONH-alkylene, -CON(alkyl)-alkylene, -NHCO-alkylene or -N(alkyl)CO-alkylene group the alkylene moiety of the above-mentioned groups optionally being substituted by one or two alkyl groups or by an aryl or heteroaryl group, or E denotes an $-N(R_{14})$-alkylene group wherein the alkylene moiety may additionally be substituted by one or two C_{1-6}-alkyl groups, by a C_{2-4}-alkenyl or C_{2-4}-alkynyl group, by a hydroxy, amino, aryl or heteroaryl group, by a C_{1-6}-alkoxy or C_{1-6}-alkylamino group, by a dialkylamino group having a total of 2 to 8 carbon atoms, or by an HNR_{13} or N-alkyl-NR_{13} group, and

vi) R_8 does not denote a hydrogen atom):

A denotes a straight-chained C_{2-3}-alkylene or C_{2-3}-alkenylene group which may additionally be substituted by one or two alkyl group or by a trifluoromethyl, aryl or arylalkyl group and wherein, additionally, a methylene group may be replaced by a carbonyl group,

a C_{5-7}-1,2-cycloalkylene or C_{5-7}-1,2-cycloalkenylene group which may be substituted by one or two alkyl groups,

a 1,2-arylene group,

a -CO-NH- or -NH-CO- group wherein the hydrogen in each case may be replaced by an alkyl, aryl or arylalkyl group, or a -CH=N- or -N=CH- group wherein the hydrogen atom in each case may be replaced by an alkyl, trifluoromethyl, aryl or arylalkyl group;

R_a and R_b, which may be identical or different, denote a hydrogen, fluorine, chlorine, brome or iodine atom or an alkyl, trifluoromethyl, alkoxy or cyano group;

R_1 and R_3 independently of each other denote a hydrogen atom or an alkyl, aryl, hydroxy, alkoxy, cyano, carboxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl or dialkylaminocarbonyl group, and

R_2, R_4, R_6 and R_8 independently of one another each denote a hydrogen atom or an alkyl group, or

R_1 together with R_2 or R_3 together with R_4 denotes an oxygen atom;

R_5 and R_7 independently of each other denote a hydrogen atom or an alkyl, aryl, carboxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl or dialkylaminocarbonyl group;

R_9 denotes a hydrogen atom, a C_{1-8}-alkyl group, a C_{3-7}-cycloalkyl group, a cycloalkylalkyl group having 3 to 7 carbon atoms in the cycloalkyl moiety and 1 to 3 carbon atoms in the alkyl moiety, an optionally aryl-substituted C_{1-6}-alkenyl group wherein the alkenyl group may not be connected to nitrogen atom via the vinyl moiety, an optionally aryl-substituted C_{3-6}-alkynyl group in which the alkynyl group may not be connected to the nitrogen atom via the ethynyl moiety, an arylalkyl or heteroarylalkyl group each having 1 to 3 carbon atoms in the alkyl moiety, a hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkylcarbonylaminoalkyl, N-alkyl-alkylcarbonylaminoalkyl, alkylsulphonylaminoalkyl,

N-alkyl-alkylsulphonylaminoalkyl, cyanoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, N-alkyl-aminocarbonylalkyl, N,N-dialkyl-aminocarbonylalkyl, alkoxycarbonyl, arylmethyloxycarbonyl, formyl, acetyl, trifluoroacetyl, 2,2,2-trifluoroethyl, or amidino group or a $R_{10}CO\text{-}O\text{-}(R_{11}CR_{12})\text{-}O\text{-}CO$- group, wherein

R_{10} denotes a C_{1-6}-alkyl group, a C_{5-7}-cycloalkyl group, an aryl group or an arylalkyl group having 1 to 3 carbon atoms in the alkyl moiety,

R_{11} denotes a hydrogen atom, an alkyl group, a C_{5-7}-cycloalkyl group or an aryl group, and

R_{12} denotes a hydrogen atom or an alkyl group;

D denotes an alkylene group,

an arylene group,

a C_{4-7}-cycloalkylene group optionally substituted by one or two alkyl groups,

or an optionally mono- or di-alkyl substituted C_{5-7}-cycloalkylene group wherein a >CH- unit is replaced by a nitrogen atom, the ring nitrogen atom being linked to a carbon atom of group E, and moreover in the above-mentioned 5- to 7-membered rings a methylene group adjacent to a nitrogen atom may be replaced by a carbonyl group;

E denotes a C_{1-6}-alkylene group which may be substituted by one or two C_{1-6}-alkyl groups, by a C_{2-4}-alkenyl or C_{2-4}-alkynyl group, by a hydroxy, amino, aryl or heteroaryl group, by a C_{1-6}-alkoxy or C_{1-6}-alkylamino group, by a dialkylamino group having a total of 2 to 8 carbon atoms, or by an HNR_{13}- or N-alkyl-NR_{13}- group, wherein

R_{13} denotes an alkylcarbonyl or alkylsulphonyl group each having 1 to 6 carbon atoms in the alkyl moiety, an alkyloxycarbonyl group having a total of 2 to 5 carbon atoms, a cycloalkylcarbonyl or cycloalkylsulphonyl group each having 5 to 7 carbon atoms in the cycloalkyl moiety, an arylalkylcarbonyl, arylalkylsulphonyl, arylalkoxycarbonyl, arylcarbonyl or arylsulphonyl group,

or E denotes an alkylene group linked to the group D via a group W, (wherein W denotes an oxygen or sulphur atom, or a sulphinyl, sulphonyl- or $-NR_{14}-$ group, wherein

R_{14} denotes a hydrogen atom, an alkyl group, a cycloalkyl, cycloalkylalkyl, cycloalkylcarbonyl or cycloalkylsulphonyl group each having 3 to 7 carbon atoms in the cycloalkyl moiety, or an aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkylcarbonyl, alkylsulphonyl, arylcarbonyl, heteroarylcarbonyl, arylsulphonyl, or heteroarylsulphonyl group),

and the alkylene group may additionally be substituted by one or two C_{1-6}-alkyl groups, by an alkenyl or alkynyl group each having 2 to 4 carbon atoms, by a hydroxy, amino, aryl or heteroaryl group, by an alkoxy or alkylamino group each having 1 to 6 carbon atoms, by a dialkylamino group having a total of 2 to 8 carbon atoms, or by an $HNR_{13}-$ or N-alkyl-$NR_{13}-$ group, wherein the heteroatom of the additional substituent is separated from a heteroatom of the group W by at least 2 carbon atoms and R_{13} is as hereinbefore defined,

or E denotes a -CONH-alkylene, -CON(alkyl)-alkylene, -NHCO-alkylene or -N(alkyl)CO-alkylene group wherein the alkylene moiety of the above-mentioned groups may be substituted in each case by one or two alkyl groups or by an aryl or heteroaryl group; and

F denotes a carbonyl group substituted by a hydroxy group, by a

C_{1-8}-alkoxy group, by an arylalkoxy group or by an $R_{15}O$- group, wherein

R_{15} denotes a C_{4-7}-cycloalkyl group or a cycloalkylalkyl group having 3 to 7 carbon atoms in the cycloalkyl moiety, a C_{9-12}-benzocycloalkyl group or an aryl group,

or F denotes an $R_{16}CO\text{-}O\text{-}CHR_{17}\text{-}O\text{-}CO$ group, wherein

R_{16} denotes a C_{1-6}-alkyl or C_{1-6}-alkoxy group, a cycloalkyl or cycloalkyloxy group each having 5 to 7 carbon atoms in the cycloalkyl moiety, an aryl, aryloxy, arylalkyl or arylalkoxy group, and

R_{17} denotes a hydrogen atom or an alkyl group,

and the shortest distance between the group F and the nitrogen atom substituted by R_9 is at least 11 bonds;

whilst, unless otherwise specified,

any aryl moiety mentioned in the definition of the above-mentioned groups may be a phenyl group which may be monosubstituted by R_{18}, mono-, di- or trisubstituted by R_{19}, or monosubstituted by R_{18} and additionally mono- or disubstituted by R_{19}, wherein the substituents may be identical or different and

R_{18} denotes a cyano, carboxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonyl, alkylcarbonyl, alkylsulphenyl, alkylsulphinyl, alkylsulphonyl, alkylsulphonyloxy, perfluoroalkyl, perfluoroalkoxy, nitro, amino, alkylamino, dialkylamino, alkylcarbonylamino, phenylalkylcarbonylamino, phenylcarbonylamino, alkylsulphonylamino, phenylalkylsulphonylamino, phenylsulphonylamino, N-alkyl-alkylcarbonylamino, N-alkyl-phenylalkylcarbonyl-

amino, N-alkyl-phenylcarbonylamino, N-alkyl-alkyl-sulphonylamino, N-alkyl-phenylalkylsulphonylamino, N-alkyl-phenylsulphonylamino, aminosulphonyl, alkylaminosulphonyl or dialkylaminosulphonyl group, and

R_{19} denotes an alkyl, hydroxy or alkoxy group or a fluorine, chlorine, bromine or iodine atom, whilst two groups R_{19}, provided that they are bound to adjacent carbon atoms, may also represent a C_{3-5}-alkylene group, a 1,3-butadiene-1,4-diylene group or a methylenedioxy group,

any arylene moiety mentioned in the definition of the above groups may be a phenylene group which may be monosubstituted by R_{18}, mono- or disubstituted by R_{19}, or monosubstituted by R_{18} and additionally monosubstituted by R_{19}, wherein the substituents may be identical or different and are defined as hereinbefore,

any heteroaryl moiety mentioned in the definition of the above groups may be a 5-membered heteroaromatic ring which contains an oxygen, sulphur or nitrogen atom, a nitrogen and an oxygen, sulphur or nitrogen atom, or two nitrogen atoms and an oxygen, sulphur or nitrogen atom, or a 6-membered heteroaromatic ring which contains 1, 2 or 3 nitrogen atoms and wherein additionally one or two -CH=N- groups may each be replaced by a -CO-NH- group, wherein

the above-mentioned heteroaromatic rings may be substituted by one or two alkyl groups or, on the carbon skeleton, by a fluorine, chlorine, bromine or iodine atom, or by a hydroxy or alkoxy group,

and unless otherwise specified the above-mentioned alkyl, alkylene or alkoxy moieties may each contain 1 to 4 carbon atoms, and each carbon atom in the above-mentioned alkylene and cycloalkylene moieties is linked to at most one heteroatom;

and the tautomers, stereoisomers and salts thereof.

3. Cyclic urea derivatives of general formula I according to claim 1, wherein (with the exception of

2-[trans-4-(2-carboxyethyl)cyclohexyl]-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-4H-1,2,4-triazol-3-one,

2-[trans-4-(2-Carboxyethyl)cyclohexyl]-4-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-4H-1,2,4-triazol-3-one,

1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(3-cyclopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

1-[1-(2-carboxyethyl)-4-piperidinyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

1-[1-(2-carboxyethyl)-4-piperidinyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one, and

1-[2-[(2-carboxyethyl)aminocarbonyl]ethyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

and with the proviso that at least one of the following conditions (i) to (vi) is satisfied

(i) A denotes a $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CO-$ or $-COCH_2-$ group substituted by one or two methyl groups, or denotes a $-C(CH_3)=N-$ group,

(ii) at least one of the groups R_1 to R_8 does not denote a hydrogen atom,

(iii) R_9 denotes a cyclopropyl, cinnamyl or 2,2,2-trifluoroethyl group, a C_{3-4}-alkynyl group, a pyridylalkyl group having 1 to 3 carbon atoms in the alkyl moiety, or an alkyl group substituted by an alkoxy, cyano, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, amino,

alkylamino, dialkylamino, alkylcarbonylamino, N-alkyl-alkylcarbonylamino, alkylsulphonylamino or N-alkyl-alkylsulphonylamino group, or R_9 denotes a C_{2-4}-alkyl group substituted by a carboxy or alkoxycarbonyl group, or a C_{3-4}-alkyl group substituted by a hydroxy group,

(iv) D denotes a 1,4-piperidinylene group optionally substituted by one or two methyl groups,

(v) E denotes an -N(R_{14})-alkylene, -CONH-alkylene or -CON(alkyl)-alkylene group wherein the alkylene moiety in each case is straight-chained and may be substituted by an alkyl, pyridyl, pyridazinyl, pyrimidinyl or pyrazinyl group or by an optionally substituted phenyl group, and

(vi) R_a does not represent a hydrogen atom):

A denotes a $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, -CH=CH-, $-CH_2CO-$ or $-COCH_2-$ group which may be substituted by one or two methyl groups,

or a -CH=N- or -N=CH- group wherein the hydrogen atom may be replaced by a methyl group;

R_a denotes a hydrogen, fluorine, chlorine, bromine or iodine atom or a methyl, trifluoromethyl, methoxy or cyano group;

R_b denotes a hydrogen atom;

R_1 and R_3 independently of each other denote a hydrogen atom or an alkyl, phenyl, hydroxy, alkoxy, cyano, carboxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl or dialkyl-aminocarbonyl group, and

R_2, R_4, R_6 and R_8 independently of one another each denote a hydrogen atom or an alkyl group, or

R_1 together with R_2 or R_3 together with R_4 denotes an oxygen

atom,

R_5 and R_7 independently of each other denote a hydrogen atom or an alkyl, phenyl, carboxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl or dialkylaminocarbonyl group;

R_9 denotes a hydrogen atom, a C_{1-6}-alkyl group, a C_{3-7}-cycloalkyl group, a cycloalkylalkyl group having 3 to 7 carbon atoms in the cycloalkyl moiety and 1 to 3 carbon atoms in the alkyl moiety, an optionally phenyl-substituted C_{3-6}-alkenyl group wherein the alkenyl group may not be connected to the nitrogen atom via the vinyl moiety, a C_{3-4}-alkynyl group wherein the alkynyl group may not be connected to the nitrogen atom via the ethynyl moiety, a phenylalkyl or pyridylalkyl group each having 1 to 3 carbon atoms in the alkyl moiety, a hydroxyalkyl, alkoxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, 2,2,2-trifluoroethyl, alkoxycarbonyl, phenylmethyloxycarbonyl, formyl, acetyl or trifluoroacetyl group or an alkyl group which is substituted by an amino, alkylamino, dialkylamino, cyano, alkylcarbonylamino, N-alkyl-alkylcarbonylamino, alkylsulphonylamino or N-alkyl-alkylsulphonylamino group;

D denotes an alkylene group,

a 1,4-phenylene group,

a 1,4-cyclohexylene group optionally substituted by one or two methyl groups,

or a 1,4-piperidinylene group optionally substituted by one or two methyl groups, wherein the ring nitrogen atom is linked to a carbon atom of group E;

E denotes a straight-chained alkylene group which may be substituted by an alkyl, phenyl, pyridyl, pyridazinyl,

pyrimidinyl or pyrazinyl group;

a straight-chained alkylene group linked to group D via a group W, wherein W denotes an oxygen or sulphur atom or a sulphinyl, sulphonyl or -NR_{14}- group, whilst the alkylene moiety may be substituted by an alkyl, phenyl, pyridyl, pyridazinyl, pyrimidinyl or pyrazinyl group and

R_{14} denotes a hydrogen atom, an alkyl group, a cycloalkyl, cycloalkyl(C_{1-3}alkyl), cycloalkylcarbonyl or cycloalkylsulphonyl group each having 3 to 7 carbon atoms in the cycloalkyl moiety, a phenyl(C_{1-3}alkyl), pyridyl(C_{1-3}-alkyl), alkylcarbonyl, alkylsulphonyl, phenylcarbonyl or phenylsulphonyl group,

or E denotes a -CONH-alkylene or -CON(alkyl)-alkylene group wherein the alkylene moiety is straight-chained and may be substituted by an alkyl, phenyl, pyridyl, pyridazinyl, pyrimidinyl or pyrazinyl group; and

F denotes a carbonyl group substituted by a hydroxy group or by a C_{1-6}-alkoxy group or by a C_{5-7}-cycloalkoxy group,

wherein the shortest distance between the group F and the nitrogen atom substituted by R_9 is at least 11 bonds; and

wherein, unless otherwise stated, the above-mentioned alkyl, alkoxy and alkylene moieties may each contain 1 to 4 carbon atoms, and

each carbon atom in the above-mentioned alkylene and cycloalkylene moieties is linked to at most one heteroatom, and

the phenyl moieties of the above-mentioned groups may each be substituted by a fluorine, chlorine or bromine atom, or by a methyl, trifluoromethyl, hydroxy or methoxy group;

and the tautomers, stereoisomers and salts thereof.

4. Cyclic urea derivatives of general formula I according to claim 1 wherein (with the exception of

2-[trans-4-(2-carboxyethyl)cyclohexyl]-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-4H-1,2,4-triazol-3-one,

2-[trans-4-(2-carboxyethyl)cyclohexyl]-4-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-4H-1,2,4-triazol-3-one,

1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(3-cyclopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

1-[1-(2-carboxyethyl)-4-piperidinyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

1-[1-(2-carboxyethyl)-4-piperidinyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one, and

1-[2-[(2-carboxyethyl)aminocarbonyl]ethyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

and with the proviso that at least one of the following conditions (i) to (vi) is satisfied

(i) A denotes a $-CH_2CH_2-$, $-CH_2CO-$ or $-COCH_2-$ group, substituted by one or two methyl groups, or denotes a $-C(CH_3)=N-$ group,

(ii) at least one of the groups R_1 to R_8 does not denote a hydrogen atom,

(iii) R_9 denotes a cyclopropyl, propargyl, cinnamyl, pyridylmethyl, 2-carboxyethyl, 2-(C_{1-4}-alkoxycarbonyl)ethyl, 2-(aminocarbonyl)ethyl, 2-(methylaminocarbonyl)ethyl, 2-(dimethylaminocarbonyl)ethyl, 2-cyanoethyl, 2-methoxyethyl,

2-aminoethyl, 2-(methylamino)ethyl, 2-(dimethylamino)ethyl, 3-hydroxypropyl, 3-aminopropyl, 3-(methylamino)propyl, 3-(dimethylamino)propyl, 3-(acetylamino)propyl, 3-(methanesulphonylamino)propyl or 2,2,2-trifluoroethyl group,

(iv) D denotes a 1,4-piperidinylene group,

(v) E denotes an $-N(R_{14})-CH_2-$ group wherein the $-CH_2-$ group may be substituted by a methyl, phenyl or pyridyl group, or

E denotes a $-CONHCH_2-$, $-CON(CH_3)CH_2-$, $-CONHCH_2CH_2-$ or $-CON(CH_3)CH_2CH_2-$group, wherein the alkylene moiety in each case may be substituted by a methyl, phenyl or pyridyl group,

(vi) R_a denotes a fluorine or chlorine atom):

A denotes a $-CH_2CH_2-$, $-CH_2CO-$ or $-COCH_2-$ group which may be substituted by one or two methyl groups,

or A denotes a $-CH=N-$ or $-N=CH-$ group, wherein the hydrogen atom may be replaced by a methyl group;

R_a denotes a hydrogen, fluorine or chlorine atom;

R_b denotes a hydrogen atom;

R_1 and R_3 independently of each other denote a hydrogen atom or a methyl, phenyl, hydroxy, methoxy, cyano, carboxy, methoxycarbonyl, ethoxycarbonyl, aminocarbonyl, methylaminocarbonyl or dimethylaminocarbonyl group, and

R_2, R_4, R_6 and R_8 independently of each other denote a hydrogen atom or a methyl group, or

R_1 together with R_2 or R_3 together with R_4 denotes an oxygen atom;

R_5 and R_7 independently of each other denote a hydrogen atom or a methyl, phenyl, carboxy, methoxycarbonyl, ethoxycarbonyl, aminocarbonyl, methylaminocarbonyl or dimethylaminocarbonyl group,

R_9 denotes a hydrogen atom, a C_{1-4}-alkyl group, a C_{3-6}-cycloalkyl group, an allyl group optionally substituted in the 3-position by a phenyl group or by one or two methyl groups, or R_9 denotes a propargyl, 2-carboxyethyl, 2-(C_{1-4}-alkoxycarbonyl)-ethyl, 2-(aminocarbonyl)ethyl, 2-(methylaminocarbonyl)ethyl, 2-(dimethylaminocarbonyl)ethyl, 2-cyanoethyl, 2-methoxyethyl, 2-aminoethyl, 2-(methylamino)ethyl, 2-(dimethylamino)ethyl, 3-hydroxypropyl, 3-aminopropyl, 3-(methylamino)propyl, 3-(dimethylamino)propyl, 3-(acetylamino)propyl, 3-(methanesulphonylamino)propyl, 2,2,2-trifluoroethyl or pyridylmethyl group;

D denotes a methylene, ethylene or 1,4-phenylene group,

a 1,4-cyclohexylene group or

a 1,4-piperidinylene group, the ring nitrogen atom being linked to a carbon atom of group E,

E denotes a straight-chained C_{1-3}-alkylene group which may be substituted by a methyl, phenyl or pyridyl group,

a methylene group linked to the group D via a group W, wherein W is an oxygen atom or an -NR_{14}- group, whilst the methylene group may be substituted by a methyl, phenyl or pyridyl group and

R_{14} denotes a hydrogen atom, a C_{1-4}-alkyl group, a cycloalkyl, cycloalkylcarbonyl or cycloalkylsulphonyl group each having 3 to 6 carbon atoms in the cycloalkyl moiety, a benzyl, alkylcarbonyl or alkylsulphonyl group each having 1 to 4 carbon atoms in the alkyl moiety, a

phenylcarbonyl or phenylsulphonyl group,

or E denotes a $-CONHCH_2-$, $-CON(CH_3)CH_2-$, $-CONHCH_2CH_2-$ or $-CON(CH_3)CH_2CH_2-$group, wherein the alkylene moiety of the above-mentioned groups may be substituted in each case by a methyl, phenyl or pyridyl group; and

F denotes a carbonyl group substituted by a hydroxy group or by a C_{1-4}-alkoxy group,

whilst the shortest distance between the group F and the nitrogen substituted by R_9 is at least 11 bonds;

and the tautomers, stereoisomers and salts thereof.

5. Cyclic urea derivatives of general formula I according to claim 1, wherein (with the exception of

2-[trans-4-(2-carboxyethyl)cyclohexyl]-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-4H-1,2,4-triazol-3-one,

2-[trans-4-(2-carboxyethyl)cyclohexyl]-4-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-5-methyl-4H-1,2,4-triazol-3-one,

1-[trans-4-(2-carboxyethyl)cyclohexyl]-3-(3-cyclopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

1-[1-(2-carboxyethyl)-4-piperidinyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

1-[1-(2-carboxyethyl)-4-piperidinyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one, and

1-[2-[(2-carboxyethyl)aminocarbonyl]ethyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one

and with the proviso that at least one of the following conditions (i) to (vi) is satisfied

(i) A denotes a $-CH_2CO-$ group substituted by one or two methyl groups or denotes a $-C(CH_3)=N-$ group,

(ii) R_9 denotes a cyclopropyl, cinnamyl, propargyl, 2,2,2-trifluoroethyl, 2-carboxyethyl, 2-(tert.butyloxycarbonyl)ethyl or 2-cyanoethyl group,

(iii) D denotes a 1,4-piperidinylene group,

(iv) E denotes an $-N(R_{14})-CH_2-$ group or a $-CONHCH_2CH_2-$ group wherein the ethylene moiety may be substituted by a methyl, phenyl or pyridyl group,

(v) R_1 or R_2 or R_1 and R_2 denote a methyl group,

(vi) R_a denotes a fluorine atom):

A denotes a $-CH_2-CH_2-$ group, a $-CH_2CO-$ group substituted by one or two methyl groups, or a $-C(CH_3)=N-$ group;

R_a denotes a hydrogen or fluorine atom;

R_b denotes a hydrogen atom;

R_1 and R_2, which may be identical or different, each denote a hydrogen atom or a methyl group;

R_3 to R_8 each denotes a hydrogen atom;

R_9 denotes a hydrogen atom or a methyl, cyclopropyl, cinnamyl, propargyl, 2,2,2-trifluoroethyl, 2-carboxyethyl, 2-(tert.butyloxycarbonyl)ethyl or 2-cyanoethyl group;

D denotes a $-CH_2-$, $-CH_2CH_2-$, 1,4-cyclohexylene group, or

a 1,4-piperidinylene group, wherein the ring nitrogen atom is linked to a carbon atom of group E;

E denotes a $-CH_2-$ group, an optionally methyl-substituted $-CH_2CH_2-$ group, or a $-CONHCH_2CH_2-$ group wherein the ethylene moiety may be substituted by a methyl, phenyl or pyridyl group,

or an $-NR_{14}-CH_2-$ group linked to the 1,4-cyclohexylene group of group D via the nitrogen atom, wherein

R_{14} denotes a hydrogen atom or a methyl, benzyl, acetyl or methanesulphonyl group; and

F denotes a carbonyl group substituted by a hydroxy, methoxy or ethoxy group,

whilst the shortest distance between the group F and the nitrogen atom substituted by R_9 is at least 11 bonds;

and the tautomers, stereoisomers and salts thereof.

6. The following cyclic urea derivatives of general formula I according to claim 1:

(1) 1-[trans-4-(carboxymethylamino)cyclohexyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

(2) 1-[trans-4-(N-methyl-N-carboxymethyl-amino)cyclohexyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

(3) 1-[trans-4-(N-benzyl-N-carboxymethyl-amino)cyclohexyl]-3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

(4) 1-[trans-4-(N-methyl-N-carboxymethyl-amino)cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

(5) 1-[trans-4-(N-benzyl-N-carboxymethyl-amino)cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

(6) 1-[trans-4-(carboxymethylamino)cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one, and

(7) 1-[trans-4-(N-acetyl-N-carboxymethyl-amino)cyclohexyl]-3-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-imidazolidin-2-one,

and the tautomers, stereoisomers and salts thereof.

7. Physiologically acceptable salts of the compounds according to at least one of claims 1 to 6 with inorganic or organic acids or bases.

8. Pharmaceutical compositions containing a compound according to at least one of claims 1 to 6 or a physiologically acceptable salt according to claim 7 optionally together with one or more inert carriers and/or diluents.

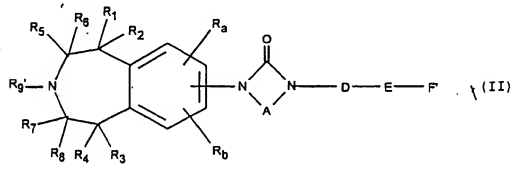
9. Use of a compound according to at least one of claims 1 to 7 for preparing a pharmaceutical composition which is suitable for combating or preventing diseases in which smaller or larger cell aggregates are involved or cell-matrix interactions play a part.

10. Process for preparing a pharmaceutical composition according to claim 8, characterised in that a compound according to at least one of claims 1 to 7 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

11. Process for preparing compounds of general formula I according to claims 1 to 7, characterised in that

a) in order to prepare compounds of general formula I, wherein R_9 is defined as in claims 1 to 6 and F represents a carboxyl group or F is defined in claims 1 to 6 and R_9 denotes a hydrogen atom:

a compound of general formula



(II)

(wherein

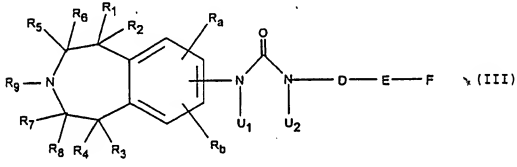
A, D, E, R_1 to R_8, R_a and R_b are defined as in claims 1 to 6, with the proviso that F' has the meanings given for F as in claims 1 to 6 and R_9' denotes a protecting group for an imino group which can be cleaved by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis, or

R_9' has the meanings given for R_9 as in claims 1 to 6 and F' denotes a group which can be converted into a carboxyl group by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis)

is converted into a compound of general formula I wherein R_9 is defined as in claims 1 to 6 and F denotes a carboxyl group or F is defined as in claims 1 to 6 and R_9 denotes a hydrogen atom, by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis; or

b) in order to prepare compounds of general formula I, wherein A denotes a straight-chained C_{2-3}-alkylene group which may additionally be substituted by one or two alkyl groups or by a trifluoromethyl, aryl or arylalkyl group and wherein, additionally, a methylene group in the terminal position is replaced by a carbonyl group;

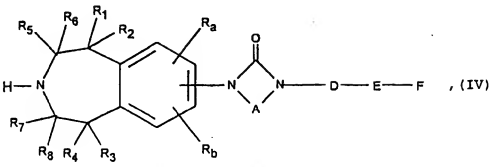
cyclizing a compound of general formula III optionally formed in the reaction mixture,



(wherein
R_1 to R_9, R_a, R_b, D, E and F are defined as in claims 1 to 6, one of the groups U_1 or U_2 denotes a hydrogen atom and the other group U_1 or U_2 denotes a straight-chained C_{2-3}-alkylene group optionally substituted by one or two alkyl groups or by a trifluoromethyl, aryl or arylalkyl group, and wherein a terminal methylene group is replaced by a Z_1-CO- group, wherein Z_1 denotes a nucleophilically exchangeable group); or

c) in order to prepare compounds of general formula I wherein R_9 denotes an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, arylalkyl or heteroarylalkyl group as mentioned in the definition of the group R_9 as in claims 1 to 6:

a compound of general formula



, (IV)

(wherein

R_1 to R_8, R_a, R_b, A, D, E and F are defined as in claims 1 to 6) is reacted with a compound of general formula

$$Z_2 - R_{20} \qquad (V)$$

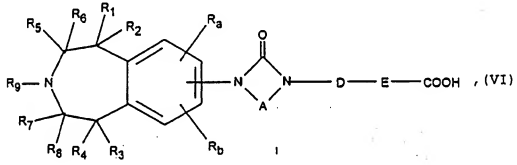
(wherein

R_{20} denotes a C_{1-6}-alkyl group, a C_{3-7}-cycloalkyl group, a cycloalkylalkyl group having 3 to 7 carbon atoms in the cycloalkyl moiety and 1 to 3 carbon atoms in the alkyl moiety, an optionally aryl-substituted C_{3-6}-alkenyl group wherein the alkenyl group may not be connected to the nitrogen atom via the vinyl moiety, an optionally aryl-substituted C_{3-6}-alkynyl group wherein the alkynyl group may not be connected to the nitrogen atom via the ethynyl moiety, an arylalkyl or heteroarylalkyl group each having 1 to 3 carbon atoms in the alkyl moiety, a hydroxyalkyl, alkoxyalkyl, 2,2,2-trifluoroethyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkylcarbonylaminoalkyl, N-alkyl-alkylcarbonylaminoalkyl, alkylsulphonylaminoalkyl, N-alkyl-alkylsulphonylaminoalkyl, cyanoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, N-alkyl-amino-carbonylalkyl or N,N-dialkyl-aminocarbonylalkyl group, wherein

the aryl moiety and the alkyl moieties are as hereinbefore defined, and
Z_2 denotes a nucleophilically exchangeable group, or Z_2 together with an adjacent hydrogen atom of the group R_{20} denotes an oxygen atom); or

d) in order to prepare compounds of general formula I wherein F denotes a carbonyl group which is substituted by a C_{1-8}-alkoxy group, by an arylalkoxy group or by an $R_{15}O$- group;

a carboxylic acid of general formula



, (VI)

(wherein
R_1 to R_9, R_a, R_b, A, D, and E are defined as in claims 1 to 6) or a reactive derivative thereof optionally prepared in the reaction mixture, is reacted with an alcohol of general formula

$$HO - R_{21} \qquad \text{(VII)}$$

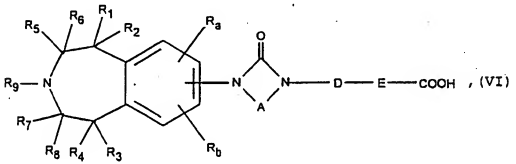
(wherein
R_{21} denotes a C_{1-8}-alkyl group, an arylalkyl group or an R_{15} group, wherein

R_{15} is a C_{4-7}-cycloalkyl group, a cycloalkylalkyl group having 3 to 7 carbon atoms in the cycloalkyl moiety, a

C_{9-12}-benzocycloalkyl group or an aryl group); or

e) in order to prepare compounds of general formula I, wherein F denotes an $R_{10}CO\text{-}O\text{-}(R_{11}CR_{12})\text{-}O\text{-}CO$- group:

a carboxylic acid of general formula



(wherein
R_1 to R_9, R_a, R_b, A, D, and E are defined as in claims 1 to 6) is reacted with a compound of general formula

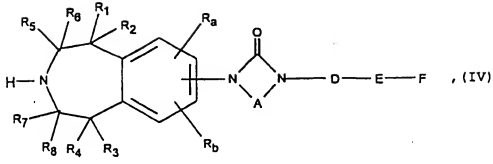
$$Z_3 - R_{12} \qquad \text{(VIII)}$$

(wherein

R_{12} denotes an $R_{10}CO\text{-}O\text{-}(R_{11}CR_{12})$- group, wherein R_{10} to R_{12} are defined as in claims 1 to 6, and
Z_3 denotes a nucleophilically exchangeable group); or

f) in order to prepare compounds of general formula I, wherein R_9 denotes a C_2-alkyl group which is substituted in the 2-position by a cyano, carboxy, alkoxycarbonyl, aminocarbonyl, N-alkyl-aminocarbonyl or N,N-dialkyl-aminocarbonyl group:

a compound of general formula



, (IV)

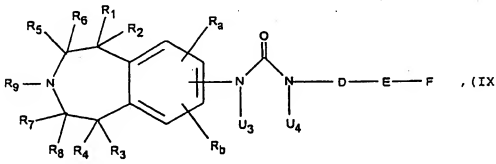
(wherein

R_1 to R_8, R_a, R_b, A, D, E and F are defined as in claims 1 to 6)

is reacted with an ethylene which is substituted by a cyano, carboxy, alkoxycarbonyl, aminocarbonyl, N-alkylaminocarbonyl or N,N-dialkylaminocarbonyl group; or

g) in order to prepare compounds of general formula I, wherein A denotes a -CH=N- or -N=CH- group optionally substituted by an alkyl, trifluoromethyl, aryl or arylalkyl group:

a compound of general formula IX optionally formed in the reaction mixture



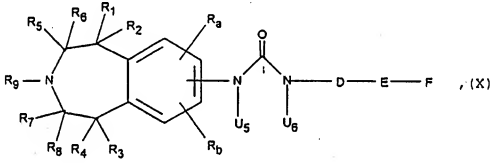
, (IX)

(wherein
R_1 to R_9, R_a, R_b, D, E and F are defined as in claims 1 to 6,

one of the groups U_3 or U_4 denotes a hydrogen atom and the other group U_3 or U_4 denotes an R_{23}-CO-NH- group, wherein R_{23} denotes a hydrogen atom or an alkyl, trifluoromethyl, aryl or aralkyl group) is cyclised; or

h) in order to prepare compounds of general formula I, wherein A denotes a straight-chained C_{2-3}-alkylene group which may additionally be substituted by one or two alkyl groups or by a trifluoromethyl, aryl or arylalkyl group:

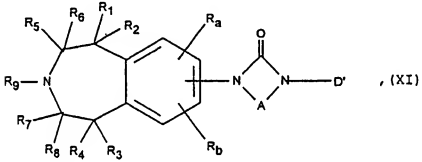
a compound of general formula X optionally formed in the reaction mixture



(wherein
R_1 to R_9, R_a, R_b, D, E and F are defined as in claims 1 to 6, one of the groups U_5 or U_6 denotes a hydrogen atom and the other group U_5 or U_6 denotes a straight-chained C_{2-3}-alkylene group optionally substituted by one or two alkyl groups or by a trifluoromethyl, aryl or aralkyl group, which may additionally be terminally substituted by a nucleophilically exchangeable group) is cyclized; or

i) in order to prepare compounds of general formula I, wherein D denotes an optionally mono- or di-alkyl substituted C_{5-7}-cycloalkylene group wherein a >CH- unit is replaced by a nitrogen atom and moreover in the above-mentioned 5- to 7-membered rings a methylene group adjacent to a nitrogen atom may be replaced by a carbonyl group:

a compound of general formula



, (XI)

I

(wherein

R_1 to R_9, R_a, R_b and A are defined as in claims 1 to 6 and D' denotes an optionally mono- or di-alkyl substituted C_{5-7}-wherein a >CH- unit is replaced by a nitrogen atom, the ring nitrogen atom being linked to a hydrogen atom, and moreover in the above-mentioned 5- to 7-membered rings a methylene group adjacent to a nitrogen atom may be replaced by a carbonyl group)

is reacted with a compound of general formula

$$Z_5\text{-}E'\text{-}F \qquad (XII)$$

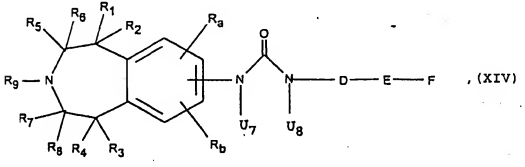
or with a compound of general formula

$$CH_2{=}CH\text{-}F \qquad (XIII)$$

(wherein
F is defined as in claims 1 to 6,
E' denotes a C_{1-6}-alkylene group which may be substituted by one or two C_{1-6}-alkyl groups, by a C_{2-4}-alkenyl or C_{2-4}-alkynyl group, by a hydroxy, amino, aryl or heteroaryl group, by an C_{1-6}-alkoxy or C_{1-6}-alkylamino group, by a dialkylamino group having a total of 2 to 8 carbon atoms, or by an HNR_{13}- or N-alkyl-NR_{13}- group, wherein R_{13} is defined as in claims 1 to 6,
Z_5 denotes a nucleophilically exchangeable group and additionally the vinyl group in a compound of general formula XIII may be substituted by one or two C_{1-6}-alkyl groups, by a C_{2-4}-alkenyl or C_{2-4}-alkynyl group or by an aryl or heteroaryl group); or

j) in order to prepare compounds of general formula I, wherein A denotes one of the straight-chained C_{2-3}-alkenylene groups as defined in claims 1 to 6, which may additionally be substituted by one or two alkyl groups, or by a trifluoromethyl, aryl or arylalkyl group:

a compound of general formula XIV optionally formed in the reaction mixture



, (XIV)

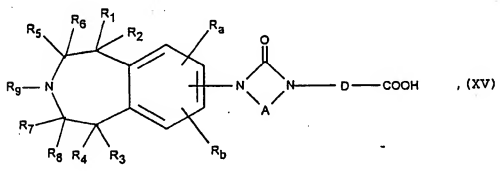
(wherein
R_1 to R_9, R_a, R_b, D, E and F are defined as in claims 1 to 6,
one of the groups U_7 or U_8 denotes a hydrogen atom and
the other group U_7 or U_8 denotes a $-(CH_2)_mHC(OR_{24})_2-$ group optionally substituted in the alkylidene moiety by one or two alkyl groups or by a trifluoromethyl, aryl or aralkyl group, wherein

m denotes the number 1 or 2 and
R_{24} denotes a C_{1-4}-alkyl group,)

is cyclised; or

k) in order to prepare compounds of general formula I, wherein E denotes a -CONH-alkylene, -CON(alkyl)-alkylene, -NHCO-alkylene or -N(alkyl)CO-alkylene group optionally substituted in the alkylene moiety:

a compound of general formula

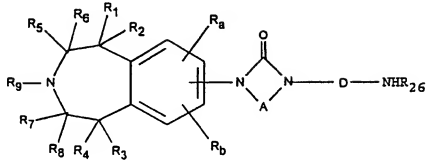


, (XV)

is reacted with an amine of general formula

$$HNR_{25} - E'' - F \qquad (XVI)$$

or an amine of general formula



is reacted with a carboxylic acid of general formula

HOOC - E" - F (XVIII)

(wherein
R_1 to R_9, R_a, R_b, A, D and F are as defined as in claims 1 to 6,
E" denotes an alkylene group optionally substituted as in claims 1 to 6, and
R_{25} and R_{26}, which may be identical or different, each denote a hydrogen atom or an alkyl group) or using a reactive derivative thereof; and

subsequently, if desired, a compound of general formula I thus obtained wherein R_{14} denotes a hydrogen atom, is converted by acylation or sulphonation into a corresponding compound of general formula I wherein R_{14} denotes an alkylcarbonyl, alkylsulphonyl, cycloalkylcarbonyl, cycloalkylsulphonyl, arylcarbonyl, heteroarylsulphonyl or heteroarylcarbonyl group, and/or

if necessary any protecting group used in the above-mentioned reactions is cleaved again and/or

if desired a compound of general formula I thus obtained is resolved into the stereoisomers thereof, and/or

a compound of general formula I thus obtained is converted into its salts, particularly for pharmaceutical use into its physiologically acceptable salts.

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